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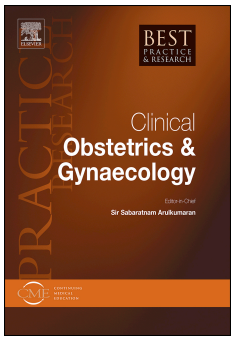


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**Title Page**

# Adjuvant treatment in cervical, vaginal and vulvar cancer

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## Abstract

Primary surgical management is successful as the sole therapeutic modality in the majority of women with early stage cervical, vaginal and vulvar cancer, but the presence of certain risk factors in the surgico-pathological specimen indicates a poorer prognosis. Adjuvant treatment can improve overall survival in such cases. Important risk factors in cervical cancer include intermediate-risk factors (large tumour size, deep cervical stromal invasion, lymph-vascular space invasion) and high-risk factors (positive or close margins, lymph nodes or parametrial involvement). In vulvar cancer, positive margins and lymph nodes are the two most important factors for adjuvant therapy. Radiation therapy has been the mainstay of adjuvant therapy in these cancers, supplemented by chemotherapy. Recent advances have seen the inclusion of newer therapeutic modalities such as immunotherapy. This review addresses the current status of various adjuvant therapeutic modalities for these gynaecological cancers.


**Key words**: Adjuvant; cervical cancer; vaginal cancer; vulval cancer; chemotherapy; radiation; immunotherapy

## Learning Objectives

- Identification of risk factors that impact the prognosis in women operated for cervical, vaginal and vulvar cancer and warrant adjuvant therapy.
- Types of adjuvant therapy
- Choosing the appropriate therapeutic strategy
- Impact on oncological outcomes

## Literature Sources

- Electronic databases: PubMed, Cochrane Library, Embase, Scopus
- Manual search of articles, references from review articles

## 1. INTRODUCTION

Adjuvant treatment is therapy that is provided after primary treatment with the aim of decreasing the risk of loco-regional and extra-pelvic cancer recurrence in cases where surgical treatment does not remove the disease completely. Radiotherapy (RT) with or without systemic therapy is the mainstay of adjuvant therapy in cervical, vaginal and vulvar cancers.

Early stages of cervical cancer (stages IA, IB1, IB2, and IIA1) are preferably treated surgically. Post-operative radiotherapy (PORT) with or without concurrent chemotherapy is indicated in patients with intermediate- and high-risk factors for recurrence to optimize overall and disease free survival (DFS). Advanced lesions (stage IB3, IIA2, III, and IV) are treated with concurrent platinum-based chemoradiation (CCRT). The role of adjuvant therapy has been also evaluated after CCRT to improve outcomes and prevent recurrences. More recently, researchers have explored the role of targeted therapy and immune check points inhibitors in cervical cancer treatment [1-6].

In vaginal and vulvar cancers, prospective randomized trials on adjuvant therapy are limited and most recommendations have been extrapolated from those of cervical cancer. The two main determinants of adjuvant therapy in these cancers are close or positive surgical margin and pathologically involved lymph nodes.

In this review we focus on various types of adjuvant therapies, their indications, and how to choose the appropriate treatment strategy in patients with cervical, vaginal and vulvar cancers.

## 2. CERVICAL CANCER

Cervical cancer is the fourth most common malignancy amongst women globally. In 2020, an estimated 604,127 new cases were diagnosed globally and about 341,831 women

died from the disease [7]. It remains a major public health problem especially in low and middle income countries (LMICs) where it is the second most frequently occurring gynaecological cancer [7].

The International Federation of Gynecology and Obstetrics (FIGO) Gynecologic Oncology Committee recently revised the staging of cervical cancer in 2018 [8]. The stage-wise management recommended by FIGO Cancer Committee is summarized in Table 1. Early stage disease (FIGO stages IA, 1B1, IB2 and IIA1) can be treated by either surgery or radiation therapy with equivalent outcomes, the choice being determined by patient factors and resource availability. Surgery is the preferred modality in younger women as it allows preservation of ovarian and sexual function. It is also preferable in some conditions such as associated fibroids, tubo-ovarian masses, etc.

Locally advanced cervical cancers are treated with CCRT. Dual therapy combining both surgery and radiation therapy is to be avoided in order to minimize morbidity and maximise resource utilization. The FIGO 2018 staging allows the use of imaging and pathological findings in addition to clinical examination to assign the stage. Any imaging modalities, i.e., ultrasound, computed tomography, magnetic resonance imaging (MRI) or positron emission tomography (PET) may be used to provide information on prognostic factors such as size of primary tumour, lymph node status, and local or distant spread. Fine needle aspiration cytology or biopsy may also be used to exclude metastases. Thus, it guides the use of the most appropriate therapeutic modality, i.e., primary CCRT in patients who are likely to require post-operative adjuvant therapy.

**Table 1: Stage-wise Management of Cervical Cancer**

| **FIGO 2018 Stage** | **Tumour size, extent** | **Treatment** |
|---|---|---|

| | | |
|---|---|---|
| IA1 | ≤ 3mm without LVSI | Cervical conization* or<br>Extrafascial hysterectomy |
| | ≤3mm with LVSI | Cervical conization* or<br>Type B RH with pelvic lymphadenectomy |
| IA2 | >3mm to ≤5mm | Conization or Radical trachelectomy* or<br>Type B RH with pelvic lymphadenectomy |
| IB1 | >5mm to ≤2cm | Radical trachelectomy* or<br>Type C RH and pelvic lymphadenectomy |
| IB2 | >2cm to ≤4cm | Type C RH and pelvic lymphadenectomy |
| IB3 | >4cm | Concurrent chemoradiation |
| IIA1 | ≤4cm, upper 2/3 vagina | Type C RH and pelvic lymphadenectomy or<br>Concurrent chemoradiation |
| IIA2 | >4cm, upper 2/3vagina | Concurrent chemoradiation |
| IIB | Parametrium involved, not up to pelvic wall | Concurrent chemoradiation |
| IIIA | Lower 1/3 vagina | Concurrent chemoradiation |
| IIIB | Lateral pelvic wall/ hydronephrosis | Concurrent chemoradiation |
| IIIC1 | Positive Pelvic LN | Concurrent chemoradiation |
| IIIC2 | Positive Para-aortic LN | Concurrent chemoradiation |
| IVA | Spread to pelvic organs | Concurrent chemoradiation or<br>Pelvic exenteration |
| IVB | Distant spread | Concurrent chemoradiation |

LVSI= Lympho-vascular space invasion; LN= Lymph node; RH= Radical hysterectomy

*If fertility is desired

### 2.1 Prognostic Factors for Early-stage Cervical Cancer

The Gynecologic Oncology Group (GOG) trial GOG 49 determined five risk factors for microscopic pelvic lymph node metastasis, namely, depth of stromal invasion, positive parametrium, lympho-vascular space invasion (LVSI), tumour grade, and gross versus occult primary tumour ($P$<0.01). The three independent risk factors for lymph node metastasis identified in stage I cervical cancer patients were LVSI, parametrial involvement and depth of invasion ($P$<0.02). On multivariate analysis, clinical tumour size, LVSI and depth of cervical stromal involvement were found to be independent predictors of disease-free interval [9]. Patients were categorized into three groups for prediction of post-operative recurrence and consideration of adjuvant therapy: low-risk (relative risk (RR) 7.5-40), intermediate-risk (RR 41-120), and high-risk (RR>120). GOG score >120 was associated with 41% recurrence rate [9].

Sedlis et al [10] reported results of GOG 92 trial which evaluated adjuvant pelvic RT versus no treatment in women with node negative early-stage (IB) cervical cancer with presence of at least two of the following factors: large tumour size (4 cm or more), deep stromal invasion (>1/3) and LVSI. Out of 277 women, 137 were randomized to pelvic external beam RT (EBRT 4600-5040 cGy) group and 140 to no further therapy (NFT) group. It was noted that RT was associated with 47% reduction in recurrence risk (RR=0.53, $P$=0.008), 88% recurrence-free rate at 2 years versus 79% in NFT group. The 5-year recurrence was 28% in NFT versus 15% in RT group.

Patients are categorized into high-, intermediate- or low-risk group depending on the presence or absence of these prognostic factors (Table 2). **High-risk factors** include positive surgical margins, lymph nodes or parametrium. The National Comprehensive Cancer Network (NCCN) guidelines recommend post-operative pelvic EBRT with concurrent

platinum-based chemotherapy with or without vaginal brachytherapy in presence of these factors [11]. **Intermediate-risk factors**, commonly referred as Sedlis criteria, are tumour size >4 cm, LVSI, and deep stromal invasion. Patients with at least two out of 3 risk factors require adjuvant RT [12,13]. Recently, tumour size >2 cm has been included as a risk factor [14,15]. Gemer et al [15] reported that 89% of patients with tumour size ≥2 cm and LVSI, 76% of patients with tumours ≥2 cm and depth of invasion >10 mm, and 87% of patients with depth of invasion >10mm as well as LVSI received adjuvant RT. They concluded that tumour size and LVSI should be taken into consideration before surgery in early-stage cervical cancer to avoid dual therapy. NCCN guidelines recommend postoperative pelvic EBRT with or without platinum-based chemotherapy in the presence of LVSI, large tumour size or deep stromal invasion but negative lymph nodes [11].

The prognostic importance of these risk factors has been evaluated in various studies [16-19]. Patients who do not have these risk factors are termed as a **low-risk group** and do not require adjuvant therapy. In addition to the above mentioned risk factors, aggressive tumour histology (e.g., adenocarcinoma) and close surgical margins should also be considered [20]. If the surgical staging included sentinel lymph node (SLN) mapping, ultra-staging for low-volume metastasis should be done [11]. Micrometastases in the SLNs alters post-operative treatment while presence of isolated tumour cells has no prognostic significance.

**Table 2 Risk stratification of patients after radical hysterectomy based on surgico-pathological factors**

| **Group** | **Risk factors** | **5-year OS rate** | **3 year recurrence risk** | **Recommended adjuvant therapy** |
|---|---|---|---|---|
| High risk | • Positive or close | 50-70% | 40% [12] | PORT with CT ± |

| | | | | |
|---|---|---|---|---|
| | surgical margins<br>• Positive lymph nodes<br>• Microscopic parametrial invasion | [12] | | Vaginal brachytherapy |
| Intermediate risk | • Large tumour size >2cm<br>• Deep stromal invasion (greater than one-third)<br>• LVSI | 89-90%<br>[21] | 30% | PORT can be considered |
| Low risk | • Small cervical tumour<br>• Negative pelvic nodes<br>• Negative parametrial invasion<br>• <1/3 stromal invasion<br>• No LVSI | 91-96%<br>[22] | | No further therapy/ Only observation |

LVSI= Lympho-vascular space invasion; PORT=Post-operative radiotherapy; CT=Chemotherapy; OS=Overall survival



**2.2 Adjuvant Treatment after Surgery in Early-stage Cervical Cancer**

Adjuvant radiotherapy with or without systemic therapy is used in the post-operative management of women with FIGO stages IA2, IB1, IB2 and IIA2 disease depending on the extent of above-mentioned adverse factors. Adjuvant treatment should ideally be started within 6 weeks of surgery and the total treatment duration should not exceed 8 weeks. Delay in initiating therapy and prolonged treatment beyond 8 weeks has been shown to have a negative impact on local control.

### 2.2.1 Adjuvant Radiotherapy after Surgery

PORT consists of whole pelvic EBRT, usually prescribed in a dose of 45-50 Gy, to adequately cover the tumour bed, and obturator, internal iliac, presacral, external iliac, common iliac lymph nodes and para-aortic lymph nodes as appropriate. Traditionally, RT has been delivered using a four-field technique and employs equally weighted antero-posterior, postero-anterior (AP-PA) and lateral beams that encompass whole pelvis based on the pelvic anatomy. In case of para-aortic lymph node involvement extended field RT (EFRT) is given [23].

The indications of vaginal brachytherapy boost following EBRT are less clearly defined but may be considered in patients with positive or close margins, large or deeply invasive tumours, parametrial or vaginal involvement, or extensive LVSI [24-25]. It is delivered to upper one third of the residual vagina using ovoids or cylinders as two weekly fractions of HDR of 6 Gy each [26].

The impact of adjuvant RT following surgery in patients with intermediate-risk disease has been analyzed by various studies that found that RT was associated with improved oncological outcomes [10,27,28]. GOG 92 indicated advantages of adjuvant RT in intermediate-risk group early-stage (IB) cervical cancer at 2 years. Further, nine year follow-up of this trial showed that adjuvant RT was associated with 46% reduction in recurrence risk (Hazard ratio (HR)=0.54 [90% CI 0.35 to 0.81], *P*=0.007) and a reduction in progression risk or death (HR=0.58 [90% CI 0.40 to 0.85], *P*=0.009). Adenocarcinoma or adenosquamous histologies had fewer recurrences relative to others with RT (HR=0.23, 90% CI 0.07 to 0.74, *P*=0.019) [27]. A retrospective study including 454 patients with early-stage cervical cancer (IB-IIA) also showed that PORT had significant advantage in DFS in patients with one or two unfavourable risk factors- parametrial invasion, deep stromal invasion and LVSI [28].

The recent Cochrane meta-analysis of two randomized control trials (RCTs) included the Bilek (1982) and GOG 92 (2006) trials. It found no significant difference in OS at five years between women who received PORT and those who received NFT (RR=0.8). PORT was associated with significantly lower risk of disease progression at five years and non-significantly higher risk of serious adverse events [29]. A GOG study reported overall 30% serious complication rate, 16% operative risk and 2% mortality associated with PORT following radical hysterectomy (RH) with lymphadenectomy in 50 patients with early-stage cervical cancer [30].

An advanced technique, intensity modulated radiation therapy (IMRT), has been suggested by American Society of Radiation Oncology (ASTRO) in order to reduce RT associated acute and late toxicity [24]. With the use of 3D conformal radiotherapy, IMRT or image-guided radiation therapy (IGRT) imaging, the morbidity to nearby parametrial and vaginal tissue can be decreased while adequately covering soft tissue regions. Folkert et al reported good oncologic outcomes in patients with early stage cervical cancer after IMRT, with DFS and OS rates over 90% at a median follow-up of 44 months with minimal toxicity [31].



**2.2.2 Adjuvant Chemoradiation after Surgery**

It was noted that women with high-risk factors who received PORT had significant reduction in loco-regional recurrences but not in OS rates which were compromised by distant recurrences [27,29]. Adjuvant CCRT is therefore recommended in this group based on results from the GOG 109/Intergroup 0107 trial which evaluated the impact of addition of four cycles of 3 weekly cisplatin 70 mg/m$^2$ and 5-fluorouracil 1000 mg/m$^2$ infusion to adjuvant RT (RT+CT) versus RT alone after RH for early-stage (IA2,1B,IIA) cervical cancer. It was determined that the addition of chemotherapy (CT) to RT after surgery significantly

improved PFS (80% in RT+CT group versus 63% in RT alone group HR=2.01, *P*=0.003) and OS (81% in RT+CT group versus 71% in RT alone group HR=1.96, *P*=0.007) when compared to RT alone in high-risk patients [12].

The Cochrane review of three RCTs including GOG 109 found that CCRT significantly reduced disease specific mortality risk (HR=0.56, 90% CI 0.36 to 0.74) and progression of disease (HR=0.47, 90% CI 0.30 to 0.74) at the cost of acute grade 4 toxicity (RR 5.66) in the high-risk patients [32].

A recent meta-analysis evaluated the role of adjuvant CCRT in patients with intermediate-risk factors and concluded that combined therapy can dramatically improve recurrence-free survival (RFS) and OS as compared with adjuvant RT alone in this group as well, with higher occurrence of grade 3/4 hematologic toxicity [33]. An open randomized phase III trial by GOG-0263 is currently ongoing and recruiting patients to evaluate RFS after post-operative adjuvant CCRT in patients with intermediate-risk factors when compared to RT alone [34].

Although a standard CT regimen has not been established in adjuvant settings, platinum-based weekly regimen (cisplatin 40 mg/m$^2$) is most widely used [11]. Three-weekly regimen is associated with higher toxicity and delayed dose as compared to weekly administration [35]. In patients with renal disease, multiple co-morbidities, advanced age or those intolerant to cisplatin, carboplatin (AUC 2 or 100 mg/m$^2$) may be used instead [36]. Another platinum-based agent which has shown a better safety profile when compared to cisplatin is nedaplatin [37-38].

Recently, consolidation CT after adjuvant CCRT has been reported to enhance local and systemic control of the disease. A recent randomized study explored the efficacy of three cycles of platinum-based consolidation CT after adjuvant CCRT in operated cases of early-stage cervical cancer with nodal disease. The study reported that there was no significant

difference in terms of DFS, OS or grade 3/4 gastrointestinal toxicity in adjuvant CCRT with consolidation group as compared to adjuvant CCRT (78.1% versus 75.4%, *P*=0.42; 83.1% versus 73.3%, *P*=0.26; 6.7% versus 4.1%, *P*=0.80, respectively). In subset of patients with >3 positive lymph nodes or patients with >2 positive lymph nodes, LVSI and deep stromal invasion, DFS and OS were better with consolidation CCRT group (*P*<0.05) [39]. Grade 3/4 hematologic side-effects were more severe in consolidation group. Currently, a phase III study, Radiation Therapy Oncology Group (RTOG) 0724, is randomizing patients with high-risk disease (parametrial or lymph node involvement) after surgery for early-stage cervical cancer to determine the impact of adding 4 cycles of carboplatin and paclitaxel CT to standard weekly cisplatin chemoradiation.

### 2.2.3 Adjuvant Chemotherapy alone

In an effort to minimize combination of therapies, the efficacy of adjuvant CT alone after primary surgical treatment in early cervical cancer has been evaluated. This is mainly used in Japan where the majority of patients undergo Okabayashi RH (corresponds to class IV hysterectomy in Piver's classification), which is associated with maximum local disease control. Mikami et al reported that 19.9% and 33.1% member institutions of the Japanese Gynecologic Oncology Group (JGOG) provided chemotherapy alone to the patients with intermediate- and high-risk respectively [40]. In a small phase III randomized trial involving 89 patients at high risk of recurrence after RH, Curtin et al reported that adjuvant therapy with chemoradiation was not superior to CT alone [41]. At present, adjuvant CT alone cannot be recommended as a routine practice.

## 2.3 Adjuvant Treatment for Advanced Stage Cervical Cancer

The role of adjuvant therapy in patients with locally advanced cervical cancer who have received definitive chemoradiation is poorly defined. Table 3 summarizes some recent studies that have evaluated the role of adjuvant CT after primary chemoradiation. A retrospective study including 159 patients with advanced stage cancer (IB-IVA) and pelvic lymph node involvement found that adjuvant CT (5-fluorouracil or paclitaxel, plus cisplatin) as compared to no adjuvant CT significantly improved 3-year PFS (80.2% and 60.4%, *P*=0.12) and distant metastasis-free survival (85.9% and 60.1%, *P*=0.04) but not OS (83.0% and 63.7%, *P*=0.17) and local control (94.0% and 81.9%, *P*=0.12) at a median follow-up of 33.8 months [42]. A prospective study involving 118 patients with FIGO stages IB2-IVA reported similar results after consolidation chemoradiation, with OS rate of 86.4% after a median follow-up of 96 months suggesting benefits of adjuvant CT in improving local and systemic disease control [43].

**Table-3 : Adjuvant CT after primary treatment for stage IIB-IVA cervical cancer: Randomized Trials**

| **Author, Year** | **No. of patients** | **Study Design** | **Results** |
|---|---|---|---|
| Lorvidhaya, 2003 [44] | 463 | Mitomycin C+5 FU+RT in both arms<br>Adjuvant : Oral 5 FU 3 cycles | Median follow-up 89 months<br>No benefit of adjuvant CT after CCRT |
| Duenas-Gonzalez, 2011 [45] | 515 | CCRT (Gemcitabine + cDDP + RT)<br>Adjuvant (Gemcitabine + cDDP)<br>Vs CCRT (cDDP) | Median follow-up 46.9 months<br>3 yr PFS : Adjuvant:74% Vs CCRT:65%, *P*<0.02<br>3 yr OS : Adjuvant:80% Vs CCRT: 69%, *P*<0.02 |

| | | | |
|---|---|---|---|
| | | | Lower failure at all sites in adjuvant arm |
| Tang, 2012 [46] | 880 | NACT : Paclitaxel + cDDP 1 cycle<br>CCRT: cDDP in both arms<br>Adjuvant CT: Paclitaxel +cDDP 2 cycles | Median follow-up 60 months<br>5 yr DFS: 63% (CCRT) Vs 75% (adjuvant), *P*<0.05<br>Lower failure at all sites in adjuvant arm |
| Tangjitgamol, 2019 [47] | 259 | CCRT: cDDP in both arms<br>Adjuvant CT: Paclitaxel/Carboplatin 3 cycles | Median follow-up 27.4 mon<br>3 yr PFS: 67% CCRT Vs 63% adjuvant CT<br>3 yr OS: 80% CCRT Vs 63% in adjuvant CT<br>Lower distal failure in adjuvant arm |

cDDP=Cisplatin; CCRT=Concurrent chemoradiation; CT=Chemotherapy; 5FU=5-flourouracil NACT=Neoadjuvant chemotherapy



The results from randomized multicentric phase III Gynecologic Cancer InterGroup (GCIG) trial, OUTBACK, were recently published and authors reported no significantly improved OS and DFS in women with locally advanced cervical cancer after four cycles of adjuvant carboplatin and paclitaxel CT following primary chemoradiation [48].

A multicentric randomized trial is underway to evaluate the role of adjuvant CT with 4 cycles of docetaxel and nedaplatin versus observation in patients with persistent HPV DNA in exfoliated cells following primary RT or chemoradiation in FIGO stage IIA2 to IVA cervical cancer [49]. Another study National Research group (NRG)-GY006, a phase II

randomized trial of RT and platinum-based CT alone or in combination with intravenous triapine in women with advanced stage cervical cancer is ongoing.

Recently a phase 1 trial has assessed safety and tolerability of therapeutic DNA vaccine (MEDI0457) in 10 patients after chemoradiation for locally advanced or recurrent cervical cancer and reported that cervical biopsies in all the patients at the end of completion of treatment and vaccination had cleared of detectable HPV DNA [50].

### 2.4 Adjuvant Treatment after Fertility Sparing Surgery

Since the age-specific incidence of cervical cancer is bimodal, women aged 30-40 years are more likely to be diagnosed with early stage disease when preservation of fertility is desired, fertility sparing surgical procedures like conization, simple or radical trachelectomy, are increasingly being performed. Although these procedures are performed with curative intent but patients should be counselled that if a recurrence develops, definitive therapy with surgery or RT will be necessary. Criteria for recommending adjuvant therapy are the same as discussed earlier. Occasionally in these patients if the margins appear close (<5mm) on final histopathology, an additional surgical procedure to remove a portion of the cervix to achieve adequate margin can be considered [51].

### 2.5 Adjuvant treatment after Inadvertent Surgery

Inadvertent simple hysterectomy (SH) in a case of invasive cervical cancer is suboptimal treatment that warrants further adjuvant therapy. The magnitude of this problem may be larger in developing countries because of several factors like lack of cervical cancer screening, improper diagnostic work up before surgery, and limited availability of dedicated cancer centres equipped with surgical and radiation oncology facilities [52]. Postoperative radiotherapy in these patients has shown to be advantageous though not as beneficial as in

patients who had undergone RH. Sharma et al in a retrospective study evaluated the role of PORT following SH (33 patients) and RH (50 patients). The 5-year RFS was significantly lower in patients who received PORT after simple hysterectomy (49% vs 72%; *P*=0.04) [52].

### 2.6 Role of molecular bio-markers

Biological markers such as insulin-like growth factor 1 receptor (IGF-1R), major vault protein (MVP) and B-cell lymphoma-2 (BCL-2) have been investigated to predict the clinical outcomes and therapeutic response in cervical cancer and may have value in future in predicting the response towards adjuvant therapy after surgery. No or fairly positive expression of IGF-1R in tumour cells has been linked with lesser loco-regional and distant recurrences as compared tumours with strong expression of IGF-1R [53]. Higher expression of MVP and BCL-2 has also been linked to poorer outcomes and poor response to treatment [54,55]. Valenciano et al suggested that tumour proteins MVP, IGF-1R and BCL-2 are important prognostic factors and their combination should be taken into account to choose individualized treatment [56]. Currently, the role of biomarkers remain investigational.

### 2.7 Targeted therapy and Immune Check point Inhibitors as Adjuvant Therapy

Many molecular pathways pertaining to cellular proliferation, neovascularization, cell cycle, extracellular matrix adhesion, apoptosis, and DNA repair have been identified as potential therapeutic targets. Vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) are up-regulated in the majority of cervical cancers [1-2]. A monoclonal antibody, bevacizumab, inhibits VEGF-A and has been used to normalize abnormal tumour vasculature, increase tumour oxygenation, and reduce interstitial fluid pressure (IFP) [3]. Addition of VEGF inhibitors reduced disease progression and

prolonged OS at the cost of increased risk of hypertension (25% versus 2%), thromboembolism (8% versus 1%) and gastrointestinal fistulas (3% versus 0%) [3,4].

EGFR over-expression has been associated with resistance to CT and RT in squamous cell carcinoma. EGFR inhibitor, gefitinib has been evaluated as maintenance therapy after completion of CCRT [5]. Recent understanding of the programmed cell death 1/programmed death ligand 1 (PD-1/PD-L1) pathway is a promising area in the treatment of locally advanced/metastatic cervical cancer. Approximately 35% of cervical squamous cell carcinoma and 17% of adenocarcinomas express PD-L1 [6].

### 2.8 Treatment Summary

The recommended treatment of early-stage and locally advanced stages of cervical cancer is shown in Figure 1.

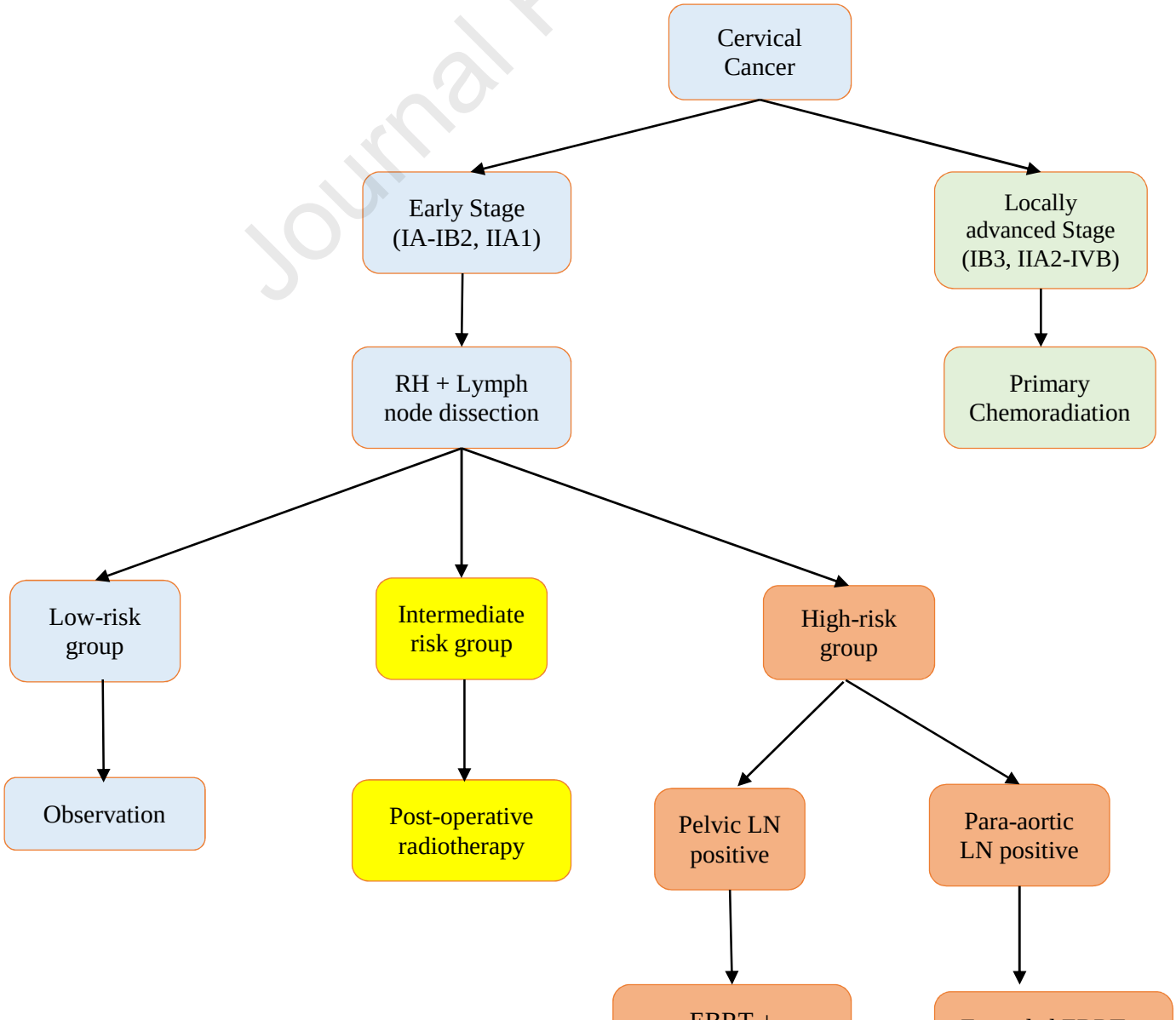

**Figure 1: Adjuvant therapy options in cervical cancer**

**2.9 Post treatment Issues**

**2.9.1 Ovarian Function-** Ovarian metastases may occur in 0.9% of cases of early-stage cervical cancer, hence they are generally left intact at the time of RH [57]. Ovarian transposition out of the RT field should be considered to preserve ovarian function. Although some protection is provided, data suggests that normal ovarian function is preserved in 20-100% of cases, depending on the type of adjuvant therapy received. A systemic review of 38 studies with a total of 765 patients evaluated ovarian survival after transposition and additional RT and concluded that ovarian survival was higher after brachytherapy (63.6-100%) as compared to EBRT (20-100%) and CCRT (0-69.2%) after a median follow-up of 7 to 102 months [58].

**2.9.2 Quality of Life (QoL) and Sexual Function-** Studies suggest that QoL may be worse amongst women who receive adjuvant therapy after RH. Acute morbidity may cause symptoms of diarrhoea, abdominal cramps, nausea, frequent micturition or bleeding from bladder or bowel mucosa. Long term consequences such as bowel stricture, stenosis or obstruction; rectovaginal fistula; vesicovaginal fistula and vaginal stenosis may occur months to years after RT is completed. In a study including 121 survivors (RH, 63; RH/CT, 38; RH/RT 20), patients in RH/RT group reported significantly lower scores on physical and social functioning as compared with patients in the RH or RH/CT group. Other gastro-intestinal and urinary symptoms were also significantly higher in RH/RT group suggesting lower QoL outcomes. Although the sexual activity

rate was significantly lower in patients in the same group but their perception of sexual pleasure was similar to other groups [59].

**2.9.3 Menopausal Hormone Therapy (MHT)-** Majority of the cancers of cervix, vagina and vulva are not oestrogen dependent and MHT can be safely considered in cervical cancer survivors who experience vasomotor symptoms, vaginal dryness or dyspareunia. MHT is neither associated with increased risk of HPV replication in genital tract nor does it promote the risk of carrying high-risk HPV DNA [60].

### 2.10 Post-treatment Surveillance

The NCCN guidelines recommend that patients should be followed-up every 3-6 months for the first 2 years, then every 6 months for the next 3-5 years [20]. Frequency of assessment depends on the risk stratification, patients with high-risk factors requires frequent assessment (3-monthly for the first 2 years). On pelvic examination, careful palpation of cardinal and uterosacral ligaments for nodularity, vaginal stenosis and suspicious areas should be noted. The supraclavicular and inguinal lymph nodes should be carefully examined. Annual vaginal cytology tests can be considered [20]. Patients should be educated regarding the symptoms (vaginal discharge or bleeding, weight loss, loss of appetite, abdominal or pelvic pain, persistent coughing) associated with recurrence at every visit. Counselling regarding healthy lifestyle, nutrition, smoking cessation, MHT and sexual health should be provided. Patients experiencing vaginal dryness and dyspareunia should be informed about the various available options. Regular vaginal intercourse, use of vaginal dilator, lubricant jelly and local oestrogen application can relieve their symptoms.

## 3. VAGINAL CANCER

Primary vaginal cancer is a rare malignancy comprising 1-2% of all gynaecological cancers. It accounted for an estimated 17,908 new cases and 7,995 deaths according to Globocan 2020 cancer statistics [7]. Large prospective trials have not been feasible due to the rarity of this condition. Most evidence comes from single institutional reports, retrospective data and clinical experience from cervical cancer. The disease is staged clinically and majority of the patients are treated by primary RT, with surgical management limited to early-stage disease confined to vaginal mucosa and paravaginal tissue (Stage I-II). Stage I well-circumscribed lesions in the upper vagina, may be treated by radical vaginectomy with lymphadenectomy. The lesions in distal vagina may require vaginectomy, vulvectomy and inguinal lymph node dissection. If the surgical margins and lymph nodes are negative, no further therapy is needed.

### 3.1 **Adjuvant Treatment in Vaginal Cancer**

Adjuvant RT is usually indicated in patients with an incomplete resection or close/positive surgical margins or pathologically involved lymph nodes. A retrospective analysis of 70 patients with early-stage (I/II) vaginal cancer reported that patients treated by surgery alone or combined surgery and RT had a significantly improved OS when compared to RT alone group ($P$<0.01) [61]. The results from another study involving 11 patients with early-stage (I/II) vagina cancer showed that stage I and selected stage II vaginal cancer patients have good OS and RFS when managed judiciously by initial surgery followed by selective adjuvant therapy [62]. Adjuvant RT has been reported to provide 5-year OS rates of 100% for stage I disease and 40%–69% for stage II disease [61,63-64].

Adjuvant RT is delivered to the pelvis with 45 Gy dose using a 4-field or anterior-posterior-posterior-anterior (AP-PA) beam arrangement similar to that in cervical cancer cases and covering pelvic lymph nodes [65]. The inferior field border must cover full vaginal

length. For cases of distal vaginal tumours, along with pelvic nodes, bilateral inguinal lymph nodes should also be covered. 3-D conformal techniques or IMRT techniques may be used to deliver RT to the primary site or involved lymph nodes but consideration should be given to movement of vagina during organ filling when planning dose [66].

Likewise there is limited experience with use of adjuvant chemoradiation in vaginal cancers. There are no prospective studies to support chemoradiation in vaginal cancer. Institutional reports support use of concurrent chemotherapy with 5-fluorouracil alone or in combination with bolus cisplatin (100 $mg/m^2$) or mitomycin C (10 $mg/m^2$) in treatment of these cancers [67]. ACR consensus panel recommends that the haemoglobin levels be maintained above >10–11 g/dL to promote tumour oxygenation [65].

## 4. VULVAR CANCER

Vulvar cancer is an uncommon cancer, accounting for 2-5% of gynaecologic cancers. Management of the patients with these cancers should be individualized taking in consideration the primary tumour and status of groin lymph nodes. Early stage disease is primarily treated surgically while CCRT can also be given depending on patient characteristics. The treatment of advanced stage disease especially in those requiring extensive radical procedures and exenteration to achieve adequate surgical margins is predominantly chemoradiation.

The surgical treatment, either radical local excision or modified radical vulvectomy with or without inguinofemoral lymphadenectomy, aims at obtaining tumour free pathological margin. The resection of 1 cm margin of grossly normal tissue and up to the deep fascia or a minimum of 1 cm deep margin are recommended by ESGO and NCCN guidelines [68]. The groin dissection is performed for stage Ib and more. Sentinel lymph

node (SLN) biopsy can be performed in unifocal tumour less than 4 cm in largest dimension without suspicious lymph nodes on clinical examination and imaging.

### 4.1 Adjuvant Treatment in Vulvar Cancer

Prospective randomized trials on adjuvant therapy after vulval cancer are limited due to rarity of this disease and most of the approaches have been extrapolated from the effective adjuvant therapies for cervical cancer. The two main determinants of adjuvant treatment include positive or close margin and lymph node metastasis. The other factors to be considered include LVSI, deep invasion of the primary lesion or large tumour size [69]. If the pathological margins are close or positive, repeat resection to obtain tumour-free adequate margins or adjuvant RT are the options available [68].

Early randomized trial, GOG 37 conducted by Homesley et al, enrolled 114 patients with positive groin nodes after surgery to receive either RT or pelvic lymphadenectomy [70]. Two-year OS was reported superior in those who received adjuvant RT as compared pelvic lymphadenectomy group (68% versus 54%, $P$=0.03). Also, the long-term follow-up (median 74 months) reported higher survival rates in patients who received adjuvant RT (51% versus 29%, $P$=0.015) with most significant benefit in those with 2 or more positive nodes or fixed ulcerated groin nodes ($P$=0.004) [71]. GOG 88 trial randomized patients with vulvar cancer without suspicious inguinal nodes to receive either groin dissection or groin RT. However, the study was closed prematurely because of excessive number of groin relapses on groin RT regimen [72].

A recent large retrospective multicentric study (AGO-CaRE-1) found adjuvant RT improves prognosis in any node positive disease [73]. Among those with pathologically involved groin nodes (n=447), 244 patients received adjuvant therapy consisting mainly of adjuvant RT (84%) and adjuvant CCRT (14%). Compared with those who did not undergo

postoperative therapy, adjuvant treatment significantly improved the 3-year PFS (40% versus 26%, respectively; HR=0.67, 95% CI 0.51-0.88). However, there was no significant improvement in OS at 3 years (57% versus 51%) [73]. Thus the indication of adjuvant RT for a single lymph node <5mm metastasis is less clearly defined.

A recent multicentric cohort study evaluated the impact of adjuvant RT on women with single intracapsular lymph node metastasis in 176 women and reported that in this sub-group of patients, LVSI is an independent risk factor associated with lesser recurrence-free survival. The study concluded that adjuvant RT should be considered irrespective of number of positive lymph nodes especially in cases of LVSI [74]. Another study by van der Velden et al analysed groin recurrence in 96 patients with single intracapsular positive nodes who did not receive adjuvant RT and observed a low risk of groin recurrence (1/96; 1%) and combined local and groin recurrence (2/96; 2.1%). They concluded that in such cases adjuvant RT can be safely omitted preventing toxicity and morbidity [75].

The current NCCN and ESGO guidelines recommend observation for patients with early stage disease (T1a). The need for adjuvant therapy is determined by the lymph node status in addition to the primary site surgery for T1b and T2 stage disease. If adequate surgical margins are not achieved, re-excision may be planned [68]. If re-excision is not feasible, EBRT or systemic therapy should be considered. If sentinel or groin lymph nodes contain metastasis, adjuvant therapy is recommended. Adjuvant therapy is indicated for any lymph node with macrometastasis (5mm or more); extracapsular spread and two or more lymph nodes with <5mm metastasis [68]. The addition of CT as a radio-sensitizer is recommended for two or more positive inguinofemoral lymph node or any lymph node with >2mm spread. When sentinel lymph nodes are positive, either RT with or without concurrent CT; or complete inguinofemoral lymph node dissection followed by EBRT with or without CT is recommended. Various guidelines recommend addition of any of the following CT

agents as a radiosensitizer either as a single agent or combination- cisplatin (preferred), carboplatin, paclitaxel, mitomycin C, 5-fluorouracil and ifosfamide. Adjuvant RT should target the primary tumour site and groins and should ideally be started within 6 weeks of surgical treatment.

**Primary Site:** Pathological features associated with high risk of local failure at primary site includes LVSI, depth of invasion >5mm, margin <8mm, and microscopically positive margin. Heaps et al. in a retrospective study have shown that surgical margin of >8mm decreases local recurrence by 50% [69]. Faul et al. observed 58% recurrence in patients with close margin (<8mm) who were kept on observation compared to 16% with RT [76]. Recently some authors have observed a greater risk of recurrence with margin ≤5mm, and radiation dose >56Gy decrease the risk of vulvar recurrence [77].

In a retrospective study of 257 patients with primary squamous vulvar cancer, the five-year OS rate among those with close or positive margins (n=192) was 29% in patients not receiving RT and 68% in those receiving RT. Among patients with negative surgical margins (n=65), RT was not associated with an OS benefit [78].

The total radiation dose should reach 56 Gy in case of close or positive margins [79]. IMRT has shown comparable response with published data in cases of vulvar cancer with decreased perineal skin, bowel and bladder toxicity [80]. The utility of integrated skin flash (ISF) planning technique for IMRT has also been described to decrease the marginal miss and account for anatomic variation, intra- and inter-fraction patient motion during treatment to improve vulval CTV and plan homogeneity [81].

**Nodal site:** Adjuvant RT to groins and pelvis is indicated for stage III-IVA lesions, 2 or more affected lymph nodes, and single node with macrometastasis or extracapsular involvement.

Adjuvant RT has shown survival benefit (2 year OS- 59% versus 31%) in patients with lymph node involvement when compared to those without adjuvant treatment [70,71,73,82].

GROINS-V II has investigated the safety of complete inguinofemoral lymphadenectomy versus adjuvant RT in early-stage vulvar cancer patients with a sentinel node metastasis ≤2 mm as well as the efficacy, safety, and short- and long-term morbidity of lymphadenectomy and RT in patients with a sentinel node metastasis >2 mm [83]. The authors suggested that RT to the groins is a safe alternative for inguinofemoral lymphadenectomy in patients with SLN metastasis ≤2 mm, with minimal toxicity and lymphadenectomy may be omitted in patients with squamous vulvar cancer <4cm and a negative SLN.

In case of positive inguinofemoral nodes, the RT field should include groin and pelvic nodal areas. If pelvic nodes are non-suspicious on imaging, the upper limit of the field is marked at the level of bifurcation of the common iliac artery. RT dose in cases of only groin node involvement should be approximately 45-50 Gy, whereas if there is extra-nodal involvement, >56 Gy may need to be delivered [79].

IMRT is strongly recommended in RT planning of vulvar cancer to minimize the morbidity to adjoining critical structures while maintaining adequate tumour coverage. Figure 2 shows RT dosimetric coverage of primary site and bilateral inguinofemoral lymph nodes. RT dose of 50 Gy is usually sufficient in cases of microscopic inguinal metastasis which may be increased upto 60 Gy when multiple lymph nodes or extracapsular extension is present.

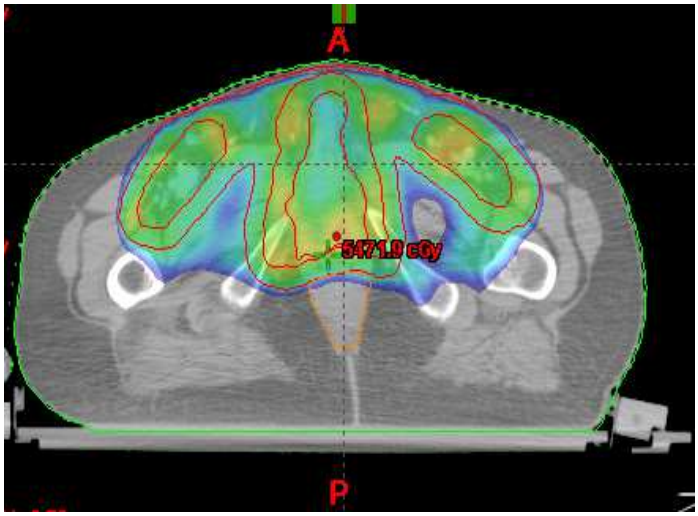


**Figure 2 CT scan image showing the RT dosimetric coverage of primary site and the bilateral inguinal femoral nodes.**



## Summary

Early-stage cervical cancer includes FIGO stages IA, IB1, IB2 and IIA1 disease which are managed by either surgery or primary chemoradiation. Presence of any high-risk factor (positive surgical margins, lymph nodes or parametrium) or any two of the three intermediate-risk factors (tumour size >2 cm, LVSI or deep stromal invasion) warrants adjuvant therapy after radical hysterectomy. For patients with high-risk factors, adjuvant chemoradiation with or without vaginal brachytherapy should be given while patients with intermediate-risk factors should receive adjuvant radiotherapy after surgery. Adjuvant chemotherapy alone should not be given in routine practice. Locally advanced cervical cancers should be treated with primary chemoradiation. There is insufficient evidence at present to recommend adjuvant therapy following primary chemoradiation.

Evidence-based data for adjuvant treatment of vaginal and vulval cancer is lacking to define practice guidelines and most of the present recommendations have been extrapolated from cervical cancer. Consideration should be given to provide adjuvant RT with platinum-based chemotherapy after surgery for vaginal cancer. The two main determinants of adjuvant treatment after surgery for vulvar cancer include positive or close margin and lymph node metastasis. Adjuvant RT to groin and pelvis along with platinum-based CT should be considered in patients with close margin or more than one involved lymph nodes. Advanced RT techniques should be utilized to decrease treatment associated bowel or bladder morbidity. Further research is needed for better characterization of oncological outcomes after administering newer therapeutic agents.



**Practice Points**

- The standard of care for high-risk group after RH for early stage cervical cancer is adjuvant PORT with concurrent CT.
- The standard of care for intermediate-risk group after RH for early stage cervical cancer is adjuvant PORT. The role of concurrent CT is currently being tested in this group.
- In early-stage vaginal cancer, adjuvant RT can be considered in presence of lymph node involvement and margin positivity.
- Use of concurrent CT with weekly cisplatin can be considered in vaginal cancer.
- Whenever available, brachytherapy should be used to deliver additional boost to the primary tumour bed.

- In vulvar cancer, adjuvant therapy is recommended in cases of close or positive margins and more than one lymph node involvement. Consider adjuvant chemoradiation in patients with two or more lymph nodes and bulky nodal disease
- MHT appears to be a safe treatment option for women with cervical and vaginal cancer.

## Research Agenda

- Phase III studies involving newer therapeutic options like altretamine or pemetrexed combined with cisplatin , pembrolizumab, erlotinib, celecoxib and bevacizumab
- Phase I/II studies exploring role of local delivery of cytotoxic agents needs to be explored
- Role of therapeutic vaccines, nano-medicine, thermo-radiotherapy as adjuvant therapy
- Use of stereotactic body RT in gynaecological malignancies
- Role of adjuvant RT in single occult intracapsular groin lymph node metastasis



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## Conflicts of interest

The authors have no conflicts of interest.

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**Multiple choice questions**

1. A 25 year old woman with cervical stage Ib1 underwent radical hysterectomy with lymph node dissection. On histopathological examination 1 x 1 x 1.5 cm squamous cell carcinoma is noted involving 0.5mm of right vaginal fornix and 2/3 cervical stroma

without parametrial extension. Lymph nodes were found to be negative. What will be the next step in management?

a. Observation
b. Adjuvant RT
c. Adjuvant chemoradiation
d. Pelvic exenteration

2. A 65-year-old lady underwent wide local excision for a well lateralized 1.5 cm unifocal labial mass. On histopathology margins are <5mm and invasion is 0.6mm. What is the next best step?

a. Observation
b. EBRT
c. Re-excision
d. Inguinofemoral lymph node dissection

3. Which of the following clinical scenarios requires adjuvant RT?

a. Tumour > 2 cm, No LVSI, superficial cervical stromal invasion
b. Tumour >2 cm, No LVSI, deep cervical stromal invasion
c. Tumour <2cm, LVSI, superficial cervical stromal invasion
d. Tumour <2cm, No LVSI, deep cervical stromal invasion

4. A 45-year-old Para 3 woman underwent Type C RH with pelvic lymphadenectomy for stage Ib2 cervical cancer with positive vaginal margins and parametrium. Which of the following should be advised next?

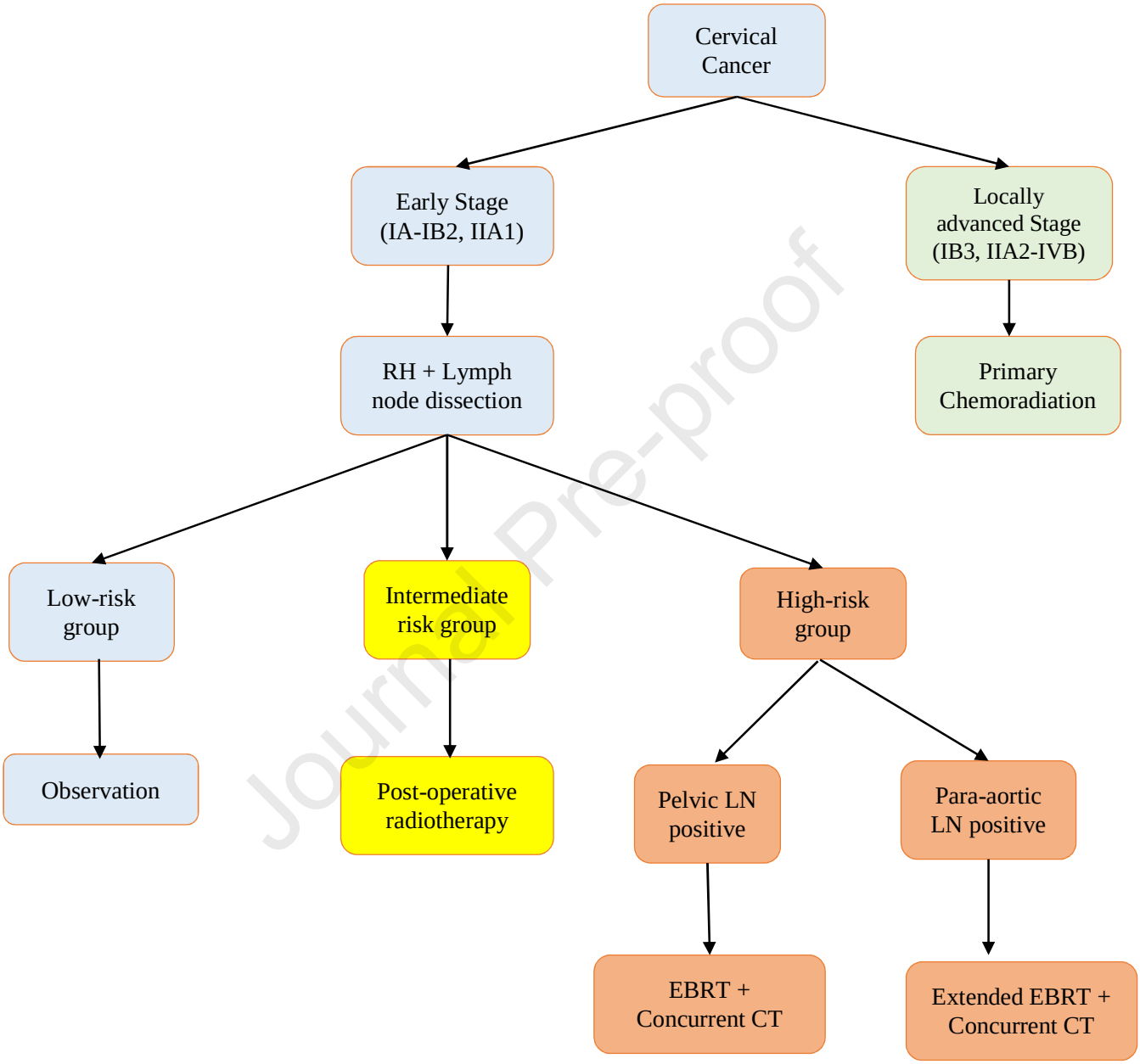
a. EBRT alone

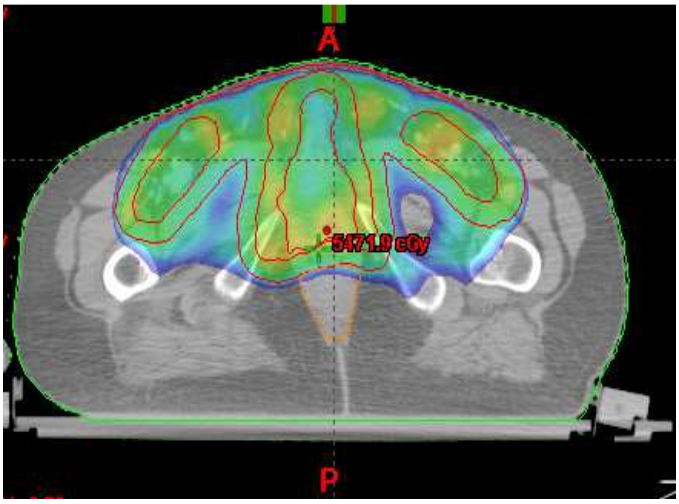
b. EBRT with concurrent CT

c. Vaginal brachytherapy with systemic CT

d. EBRT with concurrent CT with vaginal Brachytherapy

Answers: 1(a); 2(c); 3(b); 4(d)





Highlights

- Indications for adjuvant therapy following cervical cancer have been well established.
- Revised 2018 FIGO staging of cervical cancer may bring down the rate of adjuvant treatments hence avoiding dual therapy.
- Adjuvant therapy after surgery may be beneficial in vulvar cancer with nodal involvement.