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Practice Guideline

Clinical practice guidelines for cervical cancer: the Korean Society of Gynecologic Oncology guidelines

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ABSTRACT

This fifth revised version of the Korean Society of Gynecologic Oncology practice guidelines for the management of cervical cancer incorporates recent research findings and changes in treatment strategies based on version 4.0 released in 2020. Each key question was developed by focusing on recent notable insights and crucial contemporary issues in the field of cervical cancer. These questions were evaluated for their significance and impact on the current treatment and were finalized through voting by the development committee. The selected key questions were as follows: the efficacy and safety of immune checkpoint inhibitors as first- or second-line treatment for recurrent or metastatic cervical cancer; the oncologic safety of minimally invasive radical hysterectomy in early stage cervical cancer; the efficacy and safety of adjuvant systemic treatment after concurrent chemoradiotherapy in locally advanced cervical cancer; and the oncologic safety of sentinel lymph node mapping compared to pelvic lymph node dissection. The recommendations, directions, and strengths of this guideline were based on systematic reviews and meta-analyses, and were finally confirmed through public hearings and external reviews. In this study, we describe the revised practice guidelines for the management of cervical cancer.

Keywords: Chemoradiotherapy; Immune Checkpoint Inhibitors; Minimally Invasive Surgical Procedures; Practice Guideline; Sentinel Lymph Node Biopsy; Uterine Cervical Neoplasms

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Synopsis
The Korean Society of Gynecologic Oncology developed an updated practice guidelines for the management of cervical cancer. Each key questions were developed focusing on recent notable insights and crucial contemporary issues. The recommendations, directions and strength in this guideline were based on systematic reviews and meta-analyses.

INTRODUCTION

The Korean Society of Gynecologic Oncology (KSGO) has issued practice guidelines to standardize cervical cancer treatment and enhance its quality in Korea, with the ultimate goal of improving the survival rates of patients with cervical cancer. While various countries and academic organizations, including those in the United States and Europe, have issued clinical guidelines, it is essential to develop treatment guidelines tailored to the Korean healthcare environment because of the differences in medical systems, healthcare quality, and national health insurance coverage among countries. These guidelines are evidence-based and created through systematic reviews of clinical trial results and the application of objective evaluation tools. It targets gynecologic oncologists at tertiary hospitals, where patients with cervical cancer mainly receive treatment, and physicians are responsible for post-treatment follow-ups.

Cervical cancer treatment guidelines have been updated approximately every 5 years since their inception in 2006. The current version, the fifth revised edition, is based on version 4.0, which was released in 2020, and incorporates recent research findings and changes in treatment strategies.

The histopathological classification in these guidelines follows the 2020 revised World Health Organization classification [1], and the staging of cervical cancer is based on the 2018 revised International Federation of Gynecology and Obstetrics staging system (**Table 1**) [2].

MATERIALS AND METHODS

1. The committee on guideline development

The development committee of the KSGO cervical cancer practice guidelines was organized into an operating committee, working committee, advisory committee, conflict of interest committee, and an administrative support team based on the agreement and recommendations of the KSGO and the National Cancer Center. The operating committee consisted of the current executive board members of the KSGO and chairpersons of the guideline subcommittees, overseeing the planning and support for the development of these clinical practice guidelines. The working committee was responsible for evidence collection, systematic reviews, grading of the level of evidence, and manuscript writing. Methodology experts provided consultation on methodology throughout the development process. The advisory committee included eminent professors in the field of gynecologic oncology and professors recommended by relevant societies, who evaluated the applicability of clinical practice guidelines in real-world settings, and reviewed their validity from different perspectives. The conflict of interest committee conducted investigations and assessed risks according to conflict of interest management principles.

Table 1. International Federation of Gynecology and Obstetrics clinical staging for uterine cervix (2018)

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm
IA1	Measured stromal invasion <3 mm in depth
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than stage IA), lesion limited to the cervix uteri
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	Invasive carcinoma ≥4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma <4 cm in greatest dimension
IIA2	Invasive carcinoma ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum (a bullous edema, as such, does not permit a case to be allotted to stage IV)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

2. Development of key questions and literature search strategy

Key questions were developed, focusing on recent notable insights and crucial contemporary issues in the field of cervical cancer. These questions were evaluated for their significance and impact on the current treatment and were finalized through voting by the development committee. Subsequently, we defined and detailed Patient/Problem, Intervention, Comparison, Outcome (PICO) for each key question (**Table S1**). After extracting the primary keywords of each key question for PICO, we converted these keywords into search terms for each database (MeSH, free text, and Emtree) and constructed search strings (**Table S2**). The databases included in the literature search were MEDLINE, Embase, Cochrane CENTRAL, KoreaMed, and KMbase, with searches limited to Korean and English literature. Animal studies and systematic reviews were excluded. We subsequently combined the search results from the various databases and removed duplicates. The identified studies were reviewed for inclusion and exclusion criteria (**Data S1**). For the selected literature, a quality assessment was conducted using the Cochrane risk-of-bias tool for randomized trials (RoB) (version 2.0; **Data S2**). Finally, meta-analyses and systematic reviews were performed on the included literature to establish evidence for deriving the direction and strength of the recommendations (**Data S3**, **S4** and **S5**).

3. Derivation of recommendations

The recommendations were developed based on the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) Evidence to Decision framework. The factors considered in the recommendation formulation included benefits, harm, certainty of evidence, balance of effects, values, acceptability, feasibility, resource requirements, and equity (**Data S6**). The strengths of the recommendations were classified into 4 levels according to the GRADE methodology: strong for, weak/conditional for, weak/conditional against, and strong against. After drafting the initial recommendations, a consensus meeting was held, where the recommendations and their strengths were finalized through discussions and voting.

4. External review by experts

For the external review of the developed practice guidelines, an advisory committee consisting of experts from various societies related to gynecologic cancer, including the KSGO, Korean Society of Pathologists, Korean Society of Medical Oncology, Korean Society of Urogenital Radiology, Korean Society for Radiation Oncology, and Korean Society of Nuclear Medicine, conducted reviews and validity assessments. After a consensus meeting, the initial draft of the recommendations was subjected to external review by the advisory committee to gather opinions. A public hearing was organized during the 38th Annual Meeting of the KSGO in 2023 to collect as many opinions as possible. The final clinical practice guidelines were formulated after the revision process, incorporating feedback received during this phase.

CLINICAL CONSIDERATIONS AND RECOMMENDATIONS

1. KQ1. Does the addition of immune checkpoint inhibitors to primary treatment (chemotherapy +/– bevacizumab) improve the survival of patients with persistent, recurrent or metastatic cervical cancer?

Recommendation: Adding pembrolizumab to chemotherapy +/– bevacizumab is recommended for patients with persistent, recurrent or metastatic cervical cancer.

Level of evidence: High.

Strength of recommendation: Strong for.

Evidence

The literature review for this key question included one randomized phase 3 clinical trial. This study (KEYNOTE-826) involved the addition of immune checkpoint inhibitor pembrolizumab to the standard treatment [3]. In the entire group of 617 patients, the pembrolizumab group demonstrated a significant increase in progression-free survival (PFS; hazard ratio [HR]=0.65; 95% confidence interval [CI]=0.53–0.79) and overall survival (OS; HR=0.67; 95% CI=0.54–0.84) compared to the placebo group. Subgroup analysis revealed a significant improvement in both PFS (HR=0.62; 95% CI=0.50–0.77) and OS (HR=0.64; 95% CI=0.50–0.81) among patients with programmed death-ligand 1 (PD-L1) combined positive score (CPS) ≥1 (548 patients). However, for the 69 patients with CPS <1, there was no significant difference in both PFS (HR=0.94; 95% CI=0.52–1.70) and OS (HR=1.00; 95% CI0.53–1.89).

In KEYNOTE-826, grade 3 or higher complications occurred in 81.8% and 75.1% of the patients in the pembrolizumab and placebo groups, respectively. Although there was a higher trend in the pembrolizumab group, statistical significance was not proven (odds ratio [OR]=1.46; 95% CI=0.99–2.15). Grade 3 or higher complications most commonly observed in the entire patient group were anemia and neutropenia, with hyperthyroidism being more than 10% higher in the pembrolizumab group compared to the placebo group. Treatment-related toxicity led to the discontinuation of one or more drugs in 37.5% and in 26.5% of the patients in the pembrolizumab and placebo groups, respectively. Two (0.7%) and 4 (1.3%) deaths were directly related to therapeutic agents.

Consideration

In a cost-effectiveness analysis conducted in the United States, the addition of pembrolizumab to standard chemotherapy was reported to be not cost-effective, suggesting that a reduction of

approximately 55.8% in the current drug price would make it cost-effective [4]. Another study indicated that the addition of pembrolizumab to standard chemotherapy is cost-effective; however, the addition of bevacizumab along with pembrolizumab is not [5]. Considering the Korean healthcare environment and drug prices, adding pembrolizumab is expected to be cost-effective; however, no studies have investigated this thus far. Furthermore, owing to the high cost of immune checkpoint inhibitors in environments with no Korean national insurance coverage, there is a potential increase in health inequality based on socioeconomic status.

2. KQ2. Do immune checkpoint inhibitors improve the survival of patients with recurrent or metastatic cervical cancer in whom primary treatment has failed?

Recommendation: Immune checkpoint inhibitor monotherapy can be used for patients with recurrent or metastatic cervical cancer that has failed primary treatment.

Level of evidence: High.

Strength of recommendation: Weak/conditional for.

Evidence

The literature review for this key question included one randomized phase 3 clinical trial. In this study (EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9), the investigator's choice of single-agent chemotherapy and standard treatment for recurrent or metastatic cervical cancer after the failure of first-line platinum-based chemotherapy with cemiplimab, an immune checkpoint inhibitor, was compared [6]. For the population of 608 patients, the cemiplimab group showed a significant improvement in PFS (median PFS: 2.8 vs. 2.9 months; HR=0.75; 95% CI=0.63–0.89) and OS (median OS: 11.1 vs. 8.8 months; HR=0.69; 95% CI=0.56–0.84) compared to the chemotherapy group. The objective response rate for cemiplimab was 16.4% (95% CI=12.5–21.1), with 18% (95% CI=11–28) in the PD-L1 expression ≥1% group and 11% (95% CI=4–25) in the <1% group. Grade 3 or higher complications occurred in 45.0% and 53.4% of the cemiplimab and chemotherapy groups, respectively, with no statistically significant difference between the 2 groups (OR=0.77; 95% CI=0.56–1.06). Drug discontinuation due to toxicity occurred in 8.7% and 5.2% of the patients in the cemiplimab and chemotherapy groups, respectively. Grade 3 or higher immune-related adverse events were more common in the cemiplimab group (5.3%) than in the chemotherapy group (0.7%).

Consideration

In a cost-effectiveness analysis conducted in the U.S. for the EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 study, cemiplimab treatment was reported to be cost-effective for patients with squamous cell carcinoma (SCC), adenocarcinoma, and those with CPS ≥1 [7]. Although cemiplimab received approval from the Korean Ministry of Food and Drug Safety in 2022 for cutaneous SCC, it has not been introduced in Korea. Therefore, during the consensus meeting, the recommendation strength was lowered by one level considering the current status of cemiplimab availability.

3. KQ3. Does minimally invasive radical hysterectomy result in survival outcomes similar to those of open radical hysterectomy in patients with cervical cancer?

Recommendation: Consideration should be given to not performing minimally invasive radical hysterectomy in patients with cervical cancer.

Level of evidence: Moderate.
Strength of recommendation: Weak/conditional against.

Evidence

The only randomized comparative study addressing this key question is the Laparoscopic Approach to Cervical Cancer (LACC) trial [8]. This multinational, multicenter phase 3 study engaged 33 institutions globally and enrolled 631 participants. However, due to a 10.8% patient dropout rate after randomization, this study was assessed with an uncertain risk of bias (RoB 2.0), leading to an overall moderate risk of bias and a downgraded evidence level by one tier.

In the overall population, the 4.5-year disease-free survival (DFS) rates were 86.0% and 96.5% for the minimally invasive surgery (MIS) and open surgery groups, respectively; while the 3-year OS rates were 91.2% and 97.1% for the MIS and open surgery groups, respectively. Both DFS and OS were significantly lower in the MIS than in the open surgery group (3-year DFS; HR=3.74; 95% CI=1.63–8.58; 3-year OS; HR=6.00; 95% CI=1.77–20.30).

Regarding recurrence patterns, peritoneal carcinomatosis was observed in 23% (8/35) and 9% (1/11) of patients in the MIS and open surgery groups, respectively. In the per-protocol analysis, all 9 patients with peritoneal carcinomatosis underwent MIS [9].

In the subgroup analysis, both for tumors larger and smaller than 2 cm, MIS resulted in a lower DFS compared to open surgery. Analysis based on the presence of preoperative conization showed no significant difference in DFS between MIS and open surgery in patients who underwent conization (HR=1.27; 95% CI=0.39–4.17; p=0.69) [9]. The incidence of intraoperative adverse events (grade 2 or higher) did not differ significantly between the 2 treatment groups (MIS: 12% vs. open: 10%; p=0.45). Similarly, there was no significant difference in the incidence of postoperative adverse events (grade 2 or higher) between the 2 groups (MIS: 54% vs. open: 48%; p=0.14) [10].

Consideration

The most significant reason for the decreased survival rate in minimally invasive radical hysterectomy compared to open radical hysterectomy is believed to be tumor cell spillage caused by the uterine manipulator or CO_2 gas used during the minimally invasive surgical procedure [11,12]. Various efforts have been made to prevent tumor cell spillage during MIS, such as vaginal cuff closure and uterine extraction using a retrieval bag, uterine extraction through vaginal colpotomy [11], vaginal cuff resection using a laparoscopic stapler [13], and the no-look-no-touch technique [14] with several comparative clinical studies based on these efforts [15-18]. Additionally, in the LACC trial, there was no difference in survival rates between the MIS and open surgery groups when conization was performed before radical hysterectomy (HR=1.27; 95% CI=0.39–4.17; p=0.69) and similar results have been reported in several retrospective studies [19,20]. Therefore, for patients with minimal residual disease due to prior consultation for early stage cervical cancer, there is no evidence suggesting that minimally invasive radical hysterectomy has a lower survival rate than open radical hysterectomy. For these patients, the choice between minimally invasive and open hysterectomies should be discussed.

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4. KQ4. Does adjuvant systemic therapy after chemoradiotherapy and brachytherapy improve the survival of patients with locally advanced cervical cancer?

Recommendation: Consideration should be given to not administering chemotherapy or immune checkpoint inhibitors after concurrent chemoradiotherapy (CCRT) for patients with locally advanced cervical cancer.

Level of evidence: Low.

Strength of recommendation: Weak/conditional against.

Evidence

The search results for this key question identified 5 randomized phase 3 clinical trials (**Data S4**) [21-25]. All included studies were well planned, and the analysis of outcomes was conducted according to predefined protocols, minimizing the risk of bias. However, there was heterogeneity in the reported survival rates among the studies, and statistical significance was not confirmed; hence, the evidence level was downgraded to 'low.'

In the meta-analysis of survival outcomes for this key question, there was no significant difference in PFS between the CCRT plus adjuvant group and the CCRT group (HR=0.87; 95% CI=0.75–1.01). Similarly, OS did not differ significantly between the 2 groups (HR=0.88; 95% CI=0.72–1.08). The meta-analysis of treatment-related complications varied in the reporting format among studies. Three studies reported overall complications of grade 3 or above, and the analysis showed no significant difference between the 2 treatment groups (OR=2.17; 95% CI=0.66–7.18). When complications were analyzed separately by category, hematologic complications, such as neutropenia and thrombocytopenia, occurred more frequently in the CCRT plus adjuvant group than in the CCRT group. Non-hematologic complications were reported in only 2 studies, limiting the analysis, and no significant differences were observed between the groups.

Consideration

Three of the 5 studies included in this meta-analysis excluded patients with suspected para-aortic lymph node metastasis. Therefore, the potential for adjuvant therapy following CCRT to increase survival rates in patients at a high risk of recurrence cannot be conclusively ruled out. Some retrospective studies have reported that adjuvant chemotherapy after CCRT reduces recurrence in patients with cervical cancer and para-aortic lymph node involvement [26-28]. Additionally, it is necessary to await the results of future clinical studies on checkpoint inhibitors during and after CCRT, including the KEYNOTE-A18 trial (NCT04221945).

5. KQ5. Does sentinel lymph node mapping demonstrate similar survival outcomes to those of pelvic lymph node dissection in patients with cervical cancer undergoing radical hysterectomy?

Recommendation: Sentinel lymph node mapping can be selectively performed as part of the surgical treatment for patients with cervical cancer.

Level of evidence: Low.

Strength of recommendation: Weak/conditional for.

Evidence

The literature review for this key question included only one randomized phase 3 clinical trial, the SENTICOL-2 study [29]. In the survival analysis, there was no significant difference in the 4-year DFS (HR=1.48; 95% CI=0.44–4.98) and OS (HR=1.18; 95% CI=0.00–6,576.79) between the sentinel lymph node mapping and pelvic lymph node dissection groups. All grades of adverse lymphatic events were significantly lower in the sentinel lymph node mapping group than in the pelvic lymph node dissection group (31.4% vs. 55.4%; p=0.004) [30]. In the subgroup analysis, although there was no statistically significant difference in the occurrence of major lymphatic adverse events of grade 3 or above (1.2% vs. 5.9%; p=0.061), it was considered to be caused by the small number of patients experiencing adverse events.

Consideration

A limitation of the SENTICOL-2 study was the insufficient sample size for conducting survival analysis because the study design was set to confirm the primary outcome: morbidity related to lymph node dissection, making the sample size inadequate for performing the secondary outcome analysis, which was 3-year recurrence-free survival. The total number of recurrent cases was 18, with 11 and 7 in the sentinel and pelvic lymph node dissection groups, respectively. Due to these limitations, there was a moderate risk of bias, leading to the downgrading of the evidence level by one tier. Additionally, as there was no statistical significance observed in survival rates, the evidence level was downgraded by one tier, ultimately evaluating the evidence level as 'low.' Large-scale clinical studies are required to accurately assess the effect of sentinel lymph node dissection on survival. Precise insights into this matter can be gained through the results of future studies such as SENTICOL-III (NCT03386734) and SENTIX (NCT02494063).

6. KQ6. Is there a difference in accuracy between self-collected and clinician-collected samples for human papillomavirus (HPV) testing in cervical cancer screening?

Recommendation: Self-collected HPV testing is feasible for cervical cancer screening.

Level of evidence: Low.

Strength of recommendation: Weak/conditional for.

Evidence

An evaluation based on 2 meta-analyses published in 2022 was conducted [31,32]. The evidence presented in the meta-analyses was primarily based on retrospective studies rather than radomised-controlled trials, and both studies reported Cohen's kappa values within the range of 0.6–0.8 (substantial agreement).

Consideration

The literature search conducted for KQ6 revealed that the majority of recently published studies aimed to investigate the utility of a novel HPV testing product. Therefore, there were limitations in the analysis as the HPV testing methods were not standardized, with each study using different HPV tests. In Korea, with over 40 HPV tests available on the market, it poses challenges for analysis.

There was a survey study conducted on 732 Korean women, indicating significantly higher satisfaction with HPV test by self-sampling compared to satisfaction with clinician-collected

Pap tests [33]. Although issues such as HPV test validation and cost-effectiveness require further investigation, the fact that Korean women exhibit apprehension towards clinician-collected tests suggests that self-tests could present an opportunity to broaden the scope of screening. Therefore, there is an expectation that self-tests could expand the target population for screening. In Korea, with over 40 HPV products in use and minimal research conducted on the comparative superiority among these products, the situation leads to the conditional acknowledgment of HPV tests as a screening tool. Considering these circumstances, it may be premature to recognize self-collected HPV tests as a screening tool at this moment.

DISCUSSION

1. Epidemiology

Cervical cancer had a global annual incidence of 604,000 cases in 2020, with 342,000 deaths, ranking fourth in terms of both incidence and mortality among cancers in women [34]. Recent data shows a significant decline in cervical cancer incidence and mortality rates in developed countries, which has been attributed to effective screening and prevention through the HPV vaccination. However, developing countries continue to experience high incidence and mortality rates. According to data from the Korea Central Cancer Registry, cervical cancer ranked seventh among cancers affecting Korean women in 2020, with 2,998 new cases. While the incidence of cervical cancer in Korea is gradually decreasing, it remains the third most common cancer among young women aged 15–34, with an incidence rate of 4.1 cases per 100,000 people, after thyroid and breast cancers [35].

2. Risk factors

The most important risk factor for cervical cancer is persistent high-risk HPV infection. The prevalence of chronic HPV infection is approximately 10–20% in countries with a high incidence of cervical cancer and approximately 5%–10% in low-incidence countries [36]. The HPV infection rate in South Korea varies according to researchers, but is reported to be approximately 10%–15% [37-40]. HPV testing is used as a method for cervical cancer screening [41], and HPV vaccines are being used in clinical practice for cervical cancer prevention [42].

3. Diagnosis

Cervical cancer often lacks noticeable symptoms in its early stages, although it can be accompanied by increased vaginal discharge, postcoital bleeding, and occasional spotting. Cervical cancer can be screened using cytology and colposcopy, providing an accurate diagnosis through a cervical punch biopsy. Cervical conization is recommended when the depth of infiltration is difficult to assess using cervical punch biopsy or when evaluating microinvasions.

After the histopathological diagnosis of cervical cancer, routine tests such as blood tests (including complete blood count and liver and kidney function tests), urine analysis, chest radiography, and electrocardiography are performed. For staging purposes, additional tests including colposcopy, cervical punch biopsy, cervical conization, cystoscopy, sigmoidoscopy, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and PET/CT imaging are performed [43-45]. Squamous cell carcinoma-related antigen (SCC-Ag) is a useful serum tumor marker derived from squamous epithelial cells of the cervix. It is associated with tumor stage, size, depth of invasion, lymphovascular space invasion, lymph node involvement, and clinical outcomes. SCC-Ag measurements can be conducted before or during follow-up observations [46].

4. Treatment

Early stage cervical cancer

In early stage cervical cancer, the primary treatment involves surgery or radiation therapy after determining the clinical stage. For patients with stage IA1, conization or simple hysterectomy can be performed [47]. After conization, the patients are observed if there are no residual lesions on the excised surface and no lymphovascular space invasion. If lymphovascular space invasion is present or residual lesions exist on the excised surface, repeat conization, hysterectomy, or radical hysterectomy with pelvic lymph node dissection can be performed [48-50]. For IA1 cervical cancer patients who wish to conceive and have positive lymphovascular space invasion, procedures such as simple trachelectomy, conization, or radical trachelectomy are options. For stage IA2 patients, radical hysterectomy and pelvic lymph node dissection is performed. However, based on clinical judgment, pelvic radiation should also be considered. For patients with stages IA2–IB1 who wish to conceive, radical trachelectomy and pelvic lymph node dissection can be considered [51].

For patients with tumor size of 2 cm or smaller and no parametrial invasion or lymph node metastasis, less extensive procedures such as type A hysterectomy can be performed. Patients in stages IB1–2 or IIA1 undergo radical hysterectomy and pelvic lymph node dissection, with the possibility of additional para-aortic lymph node biopsy, as needed. Compared with pelvic lymph node dissection, sentinel lymph node mapping reduces complications without significantly increasing the risk of recurrence. Therefore, the procedural choice should be discussed with the patient, along with their advantages and disadvantages (KQ5; level of evidence: low; strength of recommendation: conditional for) [29,52].

In early stage cervical cancer, radical hysterectomy can be performed not only through laparotomy but also using robotic or laparoscopic approaches, and nerve-sparing radical hysterectomy can also be performed. However, according to the LACC trial published in 2018, minimally invasive radical hysterectomy resulted in shorter disease-free and OS as compared to open radical hysterectomy. Therefore, open radical hysterectomy remains the standard treatment, and the choice of surgical method should be made after discussing the advantages and disadvantages with the patient (KQ3; level of evidence: moderate; strength of recommendation: conditional against) [8].

In cases with high-risk factors after surgery (positive surgical margins, lymph node involvement, and parametrial invasion), CCRT is administered, and if there are positive findings at the surgical margins, brachytherapy is administered [52]. If there were 2 or more moderate risk factors (large tumor size, deep stromal invasion, and lymphovascular space invasion), pelvic radiation therapy is performed. However, it is advisable to await the results of the GOG-0263 clinical trial (NCT01101451) to determine whether CCRT is more effective than pelvic radiotherapy.

Locally advanced cervical cancer

In stage IB3 and IIA2 cervical cancers, radical hysterectomy resulted in survival rates similar to those of CCRT. Therefore, radical hysterectomy or CCRT can be chosen appropriately depending on the patient's clinical condition. After CCRT, additional or radical hysterectomy can be performed selectively based on clinical circumstances [53,54].

To determine the treatment approach for stage IIB or higher cervical cancer (up to IVA), assessing the involvement of the para-aortic lymph nodes is important. Surgical methods

such as extraperitoneal or laparoscopic lymph node dissection are recommended for accurate assessment. However, considering the specificities of each clinical institution, evaluation can also be conducted using imaging tests such as CT, MRI, or PET/CT [55]. Pelvic CCRT can be administered if the para-aortic lymph nodes are negative. If positive, CCRT can be performed for both the pelvic and para-aortic lymph nodes [56].

After primary treatment with CCRT in patients with locally advanced cervical cancer, consideration should be given to not giving chemotherapy or immune checkpoint inhibitors after CCRT based on current evidence, as it does not improve their survival (KQ4; level of evidence: low; strength of recommendation: conditional against) [21-23]. However, it is necessary to await the results of upcoming clinical studies related to immune checkpoint inhibitors during and after CCRT, including the KEYNOTE-A18 trial (NCT04221945).

Metastatic disease

In cases of stage IVB metastatic cervical cancer, systemic therapy is administered; however, depending on the patient's condition, radiation therapy may also be considered.

Recurrent cervical cancer

1) Pelvic recurrence

If radiation therapy has not been previously administered, CCRT should be considered, and brachytherapy should be selectively performed [57]. In contrast, pelvic exenteration can be performed in patients who have received previous radiation therapy [58]. In some cases, retreatment with radiation therapy may also be considered [59-61].

2) Extrapelvic recurrence

Patients with extrapelvic, para-aortic, multiple, or unresectable recurrences should undergo systemic chemotherapy or supportive therapy. Isolated recurrence may be considered for selective treatment options, including chemotherapy, surgical resection, radiation therapy, and CCRT [62,63].

Systemic treatment for recurrent/metastatic cervical cancer

Systemic chemotherapy is recommended for patients with advanced or recurrent cervical cancer who are not candidates for radiation therapy or pelvic exenteration. Platinum-based combination chemotherapy is recommended as the primary treatment for advanced or recurrent cervical cancer, and the addition of bevacizumab can increase survival rates when they are used in combination [64]. Furthermore, the immune checkpoint inhibitor pembrolizumab, when added to or used as maintenance therapy alongside platinum-based combination chemotherapy, has demonstrated improved PFS and OS rates in patients with cervical cancer who have a PD-L1 CPS ≥1 (KQ1; level of evidence: strong; strength of recommendation: strong for) [3].

Palliative chemotherapy can be attempted in cases of advanced or recurrent cervical cancer with failed primary treatment, although its effectiveness is limited [65]. In the case of immune checkpoint inhibitors, cemiplimab has demonstrated superior survival rates and duration of response compared to conventional single-agent chemotherapy in patients with cervical cancer who have failed first-line treatment. However, cemiplimab is not currently available in Korea. Pembrolizumab and nivolumab have been approved for use in patients with SCC or PD-L1 positive status (KQ2; level of evidence: strong; strength of recommendation: conditional for) [66,67]. Patients with refractory cervical cancer require a

comprehensive approach tailored to their individual circumstances, including palliative care, pain management, and psychological support.

5. Follow-up

The principle for patient follow-up is every 3–4 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter, with adjustments based on the clinical status and circumstances. At each visit, a physical examination, including medical history review and pelvic examination, should be conducted. Although cervical cytology is recommended annually, it can be performed at each visit. Cervical cytology, laboratory tests, pelvic/abdominal/thoracic CT, MRI, PET scans, and serum tumor marker tests can be selectively performed based on clinical circumstances [68]. PET/CT is helpful in cases in which recurrence is not detected using conventional imaging, when the status of recurrence is unclear, or when confirming its extent.

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SUPPLEMENTARY MATERIALS

Table S1
The PICOs for key questions

Table S2
Search strategies

Data S1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart

Data S2
Risk of Bias (RoB 2.0) table

Data S3
Meta-analyses of each key questions

Data S4
Characteristics of the included studies

Data S5
GRADE evidence profiles

Data S6
Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) summary of judgements table

REFERENCES

1. World Health Organization (WHO) Classification of Tumours Editorial Board. Female genital tumours: WHO classification of tumours, 5th edition, volume 4. Lyon: IARC; 2020.
2. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. Int J Gynaecol Obstet 2018;143 Suppl 2:22-36. PUBMED | CROSSREF
3. Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. N Engl J Med 2021;385:1856-67. PUBMED | CROSSREF
4. Shi Y, Chen J, Shi B, Liu A. Cost-effectiveness analysis of pembrolizumab for treatment of US patients with persistent, recurrent, or metastatic cervical cancer. Gynecol Oncol 2022;164:379-85. PUBMED | CROSSREF
5. Barrington DA, Riedinger C, Haight PJ, Tubbs C, Cohn DE. Pembrolizumab with or without bevacizumab for recurrent or metastatic cervical cancer: a cost-effectiveness analysis. Gynecol Oncol 2022;165:500-5. PUBMED | CROSSREF
6. Tewari KS, Monk BJ, Vergote I, Miller A, de Melo AC, Kim HS, et al. Survival with cemiplimab in recurrent cervical cancer. N Engl J Med 2022;386:544-55. PUBMED | CROSSREF
7. Liu K, Zhu Y, Zhou Y, Zhu H. Cemiplimab as second-line therapy for patients with recurrent cervical cancer: a United States-based cost-effectiveness analysis. Adv Ther 2023;40:1838-49. PUBMED | CROSSREF
8. Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. N Engl J Med 2018;379:1895-904. PUBMED | CROSSREF
9. Ramirez PT, Robledo KP, Frumovitz M, Pareja R, Ribeiro R, Lopez A, et al. LACC Trial Multicenter, Randomized, Phase 3, Non-Inferiority Trial: Final Analysis on Overall Survival Comparing Open vs Minimally Invasive Radical Hysterectomy for Early Cervical Cancer. SSRN. Forthcoming 2023. CROSSREF
10. Frumovitz M, Obermair A, Coleman RL, Pareja R, Lopez A, Ribero R, et al. Quality of life in patients with cervical cancer after open versus minimally invasive radical hysterectomy (LACC): a secondary outcome of a multicentre, randomised, open-label, phase 3, non-inferiority trial. Lancet Oncol 2020;21:851-60. PUBMED | CROSSREF
11. Kong TW, Chang SJ, Piao X, Paek J, Lee Y, Lee EJ, et al. Patterns of recurrence and survival after abdominal versus laparoscopic/robotic radical hysterectomy in patients with early cervical cancer. J Obstet Gynaecol Res 2016;42:77-86. PUBMED | CROSSREF
12. Chiva L, Zanagnolo V, Querleu D, Martin-Calvo N, Arévalo-Serrano J, Căpîlna ME, et al. SUCCOR study: an international European cohort observational study comparing minimally invasive surgery versus open abdominal radical hysterectomy in patients with stage IB1 cervical cancer. Int J Gynecol Cancer 2020;30:1269-77. PUBMED | CROSSREF
13. Boyraz G, Karalok A, Basaran D, Turan T. Vaginal closure with EndoGIA to prevent tumor spillage in laparoscopic radical hysterectomy for cervical cancer. J Minim Invasive Gynecol 2019;26:602. PUBMED | CROSSREF
14. Fusegi A, Kanao H, Ishizuka N, Nomura H, Tanaka Y, Omi M, et al. Oncologic outcomes of laparoscopic radical hysterectomy using the no-look no-touch technique for early stage cervical cancer: a propensity score-adjusted analysis. Cancers (Basel) 2021;13:6097. PUBMED | CROSSREF
15. Wu X, Qiu L, Lou W, Wang X, Zhu T, Zhang Y, et al. A multicenter non-inferior randomized controlled study comparing the efficacy of laparoscopic versus abdominal radical hysterectomy for cervical cancer (stages IB1, IB2, and IIA1): study protocol of the LAUNCH 2 trial. Trials 2022;23:269. PUBMED | CROSSREF
16. Park SJ, Kong TW, Kim T, Lee M, Choi CH, Shim SH, et al. Safety and efficacy study of laparoscopic or robotic radical surgery using an endoscopic stapler for inhibiting tumour spillage of cervical malignant neoplasms evaluating survival (SOLUTION): a multi-centre, open-label, single-arm, phase II trial protocol. BMC Cancer 2022;22:331. PUBMED | CROSSREF
17. Falconer H, Palsdottir K, Stalberg K, Dahm-Kähler P, Ottander U, Lundin ES, et al. Robot-assisted approach to cervical cancer (RACC): an international multi-center, open-label randomized controlled trial. Int J Gynecol Cancer 2019;29:1072-6. PUBMED | CROSSREF
18. Bixel KL, Leitao MM, Chase DM, Quick A, Lim PC, Eskander RN, et al. ROCC/GOG-3043: a randomized non-inferiority trial of robotic versus open radical hysterectomy for early-stage cervical cancer. J Clin Oncol 2022;40 16_suppl:TPS5605. CROSSREF
19. Kim SI, Choi BR, Kim HS, Chung HH, Kim JW, Park NH, et al. Cervical conization before primary radical hysterectomy has a protective effect on disease recurrence in early cervical cancer: a two-center matched cohort study according to surgical approach. Gynecol Oncol 2022;164:535-42. PUBMED | CROSSREF

20. Han L, Chen Y, Zheng A, Chen H. Effect of preoperative cervical conization before hysterectomy on survival and recurrence of patients with cervical cancer: a systematic review and meta-analysis. Gynecol Oncol 2023;174:167-74. PUBMED | CROSSREF
21. Dueñas-González A, Zarbá JJ, Patel F, Alcedo JC, Beslija S, Casanova L, et al. Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. J Clin Oncol 2011;29:1678-85. PUBMED | CROSSREF
22. Tangjitgamol S, Tharavichitkul E, Tovanabutra C, Rongsriyam K, Asakij T, Paengchit K, et al. A randomized controlled trial comparing concurrent chemoradiation versus concurrent chemoradiation followed by adjuvant chemotherapy in locally advanced cervical cancer patients: ACTLACC trial. J Gynecol Oncol 2019;30:e82. PUBMED | CROSSREF
23. Mileshkin LR, Moore KN, Barnes E, Gebski V, Narayan K, Bradshaw N, et al. Adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone: The randomized phase III OUTBACK Trial (ANZGOG 0902, RTOG 1174, NRG 0274). J Clin Oncol 2021;39 18_suppl:LBA3. CROSSREF
24. Monk B, Toita T, Wu X, Limón JC, Zhou Q, Tarnawski R, et al. O001/#504 Durvalumab, in combination with and following chemoradiotherapy, in locally advanced cervical cancer: results from the phase 3 international, randomized, double-blind, placebo-controlled calla trial. Int J Gynecol Cancer 2022;32:A2-3. CROSSREF
25. Fujiwara K, Nishio S, Yamamoto K, Fujiwara H, Itagaki H, Nagai T, et al. LBA31 Randomized phase III trial of maintenance chemotherapy with tegafur-uracil versus observation following concurrent chemoradiotherapy for locally advanced cervical cancer, GOTIC-002 LUFT trial. Ann Oncol 2022;33:S1398. CROSSREF
26. Abe A, Furumoto H, Nishimura M, Irahara M, Ikushima H. Adjuvant chemotherapy following concurrent chemoradiotherapy for uterine cervical cancer with lymphadenopathy. Oncol Lett 2012;3:571-6. PUBMED | CROSSREF
27. Wu N, Su X, Song H, Li Y, Gu F, Sun X, et al. A multi-institutional retrospective analysis of oncologic outcomes for patients with locally advanced cervical cancer undergoing platinum-based adjuvant chemotherapy after concurrent chemoradiotherapy. Cancer Contr 2021;28:1073274821989307. PUBMED | CROSSREF
28. Yuan Y, You J, Li X, Wang W. Adjuvant chemotherapy after radiotherapy or concurrent chemoradiotherapy for pelvic lymph node-positive patients with locally advanced cervical cancer: a propensity score matching analysis. Int J Gynecol Cancer 2022;32:21-7. PUBMED | CROSSREF
29. Favre G, Guani B, Balaya V, Magaud L, Lecuru F, Mathevet P. Sentinel lymph-node biopsy in early-stage cervical cancer: the 4-year follow-up results of the Senticol 2 Trial. Front Oncol 2021;10:621518. PUBMED | CROSSREF
30. Mathevet P, Lécuru F, Uzan C, Boutitie F, Magaud L, Guyon F, et al. Sentinel lymph node biopsy and morbidity outcomes in early cervical cancer: results of a multicentre randomised trial (SENTICOL-2). Eur J Cancer 2021;148:307-15. PUBMED | CROSSREF
31. Arbyn M, Castle PE, Schiffman M, Wentzensen N, Heckman-Stoddard B, Sahasrabuddhe VV. Meta-analysis of agreement/concordance statistics in studies comparing self- vs clinician-collected samples for HPV testing in cervical cancer screening. Int J Cancer 2022;151:308-12. PUBMED | CROSSREF
32. Sy F, Greuel M, Winkler V, Bussmann H, Bärnighausen T, Deckert A. Accuracy of HPV testing on self-collected and clinician-collected samples for different screening strategies in African settings: a systematic review and meta-analysis. Gynecol Oncol 2022;166:358-68. PUBMED | CROSSREF
33. Shin HY, Lee B, Hwang SH, Lee DO, Sung NY, Park JY, et al. Evaluation of satisfaction with three different cervical cancer screening modalities: clinician-collected Pap test vs. HPV test by self-sampling vs. HPV test by urine sampling. J Gynecol Oncol 2019;30:e76. PUBMED | CROSSREF
34. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-49. PUBMED | CROSSREF
35. Division of Cancer Registration & Surveillance National Council on Compensation Insurance, National Cancer Center (KR). Annual report of cancer statistics in Korea in 2020. Goyang: National Cancer Center; 2022.
36. Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, et al. Global burden of human papillomavirus and related diseases. Vaccine 2012;30 Suppl 5:F12-23. PUBMED | CROSSREF
37. Shin HR, Lee DH, Herrero R, Smith JS, Vaccarella S, Hong SH, et al. Prevalence of human papillomavirus infection in women in Busan, South Korea. Int J Cancer 2003;103:413-21. PUBMED | CROSSREF
38. Kim YT. Current status of cervical cancer and HPV infection in Korea. J Gynecol Oncol 2009;20:1-7. PUBMED | CROSSREF

39. Oh JK, Franceschi S, Kim BK, Kim JY, Ju YH, Hong EK, et al. Prevalence of human papillomavirus and Chlamydia trachomatis infection among women attending cervical cancer screening in the Republic of Korea. Eur J Cancer Prev 2009;18:56-61. PUBMED | CROSSREF
40. Kim K, Kim JJ, Kim SM, No JH, Kim YB. Prevalence and determinants of high-risk human papillomavirus infection in women with high socioeconomic status in Seoul, Republic of Korea. Asian Pac J Cancer Prev 2012;13:269-73. PUBMED | CROSSREF
41. Kong TW, Kim M, Kim YH, Kim YB, Kim J, Kim JW, et al. High-risk human papillomavirus testing as a primary screening for cervical cancer: position statement by the Korean Society of Obstetrics and Gynecology and the Korean Society of Gynecologic Oncology. J Gynecol Oncol 2020;31:e31. PUBMED | CROSSREF
42. Cho HW, Min KJ, Kwon SH, Kim K, Kim S, Seong SJ, et al. Updated clinical guideline for human papillomavirus vaccine: the Korean Society of Gynecologic Oncology guidelines. J Gynecol Oncol 2021;32:e94. PUBMED | CROSSREF
43. Chung HH, Kang KW, Cho JY, Kim JW, Park NH, Song YS, et al. Role of magnetic resonance imaging and positron emission tomography/computed tomography in preoperative lymph node detection of uterine cervical cancer. Am J Obstet Gynecol 2010;203:156.e1-5. PUBMED | CROSSREF
44. Lv K, Guo HM, Lu YJ, Wu ZX, Zhang K, Han JK. Role of 18F-FDG PET/CT in detecting pelvic lymph-node metastases in patients with early-stage uterine cervical cancer: comparison with MRI findings. Nucl Med Commun 2014;35:1204-11. PUBMED | CROSSREF
45. Bhatla N, Berek JS, Cuello Fredes M, Denny LA, Grenman S, Karunaratne K, et al. Revised FIGO staging for carcinoma of the cervix uteri. Int J Gynaecol Obstet 2019;145:129-35. PUBMED | CROSSREF
46. Duk JM, Groenier KH, de Bruijn HW, Hollema H, ten Hoor KA, van der Zee AG, et al. Pretreatment serum squamous cell carcinoma antigen: a newly identified prognostic factor in early-stage cervical carcinoma. J Clin Oncol 1996;14:111-8. PUBMED | CROSSREF
47. Koliopoulos G, Sotiriadis A, Kyrgiou M, Martin-Hirsch P, Makrydimas G, Paraskevaidis E. Conservative surgical methods for FIGO stage IA2 squamous cervical carcinoma and their role in preserving women's fertility. Gynecol Oncol 2004;93:469-73. PUBMED | CROSSREF
48. Bekkers RL, Keyser KG, Bulten J, Hanselaar AG, Schijf CP, Boonstra H, et al. The value of loop electrosurgical conization in the treatment of stage IA1 microinvasive carcinoma of the uterine cervix. Int J Gynecol Cancer 2002;12:485-9. PUBMED | CROSSREF
49. Itsukaichi M, Kurata H, Matsushita M, Watanabe M, Sekine M, Aoki Y, et al. Stage Ia1 cervical squamous cell carcinoma: conservative management after laser conization with positive margins. Gynecol Oncol 2003;90:387-9. PUBMED | CROSSREF
50. Mota F. Microinvasive squamous carcinoma of the cervix: treatment modalities. Acta Obstet Gynecol Scand 2003;82:505-9. PUBMED | CROSSREF
51. Bernardini M, Barrett J, Seaward G, Covens A. Pregnancy outcomes in patients after radical trachelectomy. Am J Obstet Gynecol 2003;189:1378-82. PUBMED | CROSSREF
52. Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P, et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet 1997;350:535-40. PUBMED | CROSSREF
53. Cibula D, Dostalek L, Hillemanns P, Scambia G, Jarkovsky J, Persson J, et al. Completion of radical hysterectomy does not improve survival of patients with cervical cancer and intraoperatively detected lymph node involvement: ABRAX international retrospective cohort study. Eur J Cancer 2021;143:88-100. PUBMED | CROSSREF
54. Yang J, Yang J, Cao D, Shen K, Ma J, Zhang F. Completion hysterectomy after chemoradiotherapy for locally advanced adeno-type cervical carcinoma: updated survival outcomes and experience in post radiation surgery. J Gynecol Oncol 2020;31:e16. PUBMED | CROSSREF
55. Choi HJ, Ju W, Myung SK, Kim Y. Diagnostic performance of computer tomography, magnetic resonance imaging, and positron emission tomography or positron emission tomography/computer tomography for detection of metastatic lymph nodes in patients with cervical cancer: meta-analysis. Cancer Sci 2010;101:1471-9. PUBMED | CROSSREF
56. Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 1999;340:1137-43. PUBMED | CROSSREF
57. Haasbeek CJ, Uitterhoeve AL, van der Velden J, González DG, Stalpers LJ. Long-term results of salvage radiotherapy for the treatment of recurrent cervical carcinoma after prior surgery. Radiother Oncol 2008;89:197-204. PUBMED | CROSSREF
58. Chiva LM, Lapuente F, González-Cortijo L, González-Martín A, Rojo A, García JF, et al. Surgical treatment of recurrent cervical cancer: state of the art and new achievements. Gynecol Oncol 2008;110:S60-6. PUBMED | CROSSREF

59. Randall ME, Evans L, Greven KM, McCunniff AJ, Doline RM. Interstitial reirradiation for recurrent gynecologic malignancies: results and analysis of prognostic factors. Gynecol Oncol 1993;48:23-31. PUBMED | CROSSREF
60. Wang CJ, Lai CH, Huang HJ, Hong JH, Chou HH, Huang KG, et al. Recurrent cervical carcinoma after primary radical surgery. Am J Obstet Gynecol 1999;181:518-24. PUBMED | CROSSREF
61. Jhingran A. Potential advantages of intensity-modulated radiation therapy in gynecologic malignancies. Semin Radiat Oncol 2006;16:144-51. PUBMED | CROSSREF
62. Friedlander M, Grogan M; U.S. Preventative Services Task Force. Guidelines for the treatment of recurrent and metastatic cervical cancer. Oncologist 2002;7:342-7. PUBMED | CROSSREF
63. Dreyer G, Snyman LC, Mouton A, Lindeque BG. Management of recurrent cervical cancer. Best Pract Res Clin Obstet Gynaecol 2005;19:631-44. PUBMED | CROSSREF
64. Tewari KS, Sill MW, Long HJ 3rd, Penson RT, Huang H, Ramondetta LM, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med 2014;370:734-43. PUBMED | CROSSREF
65. Boussios S, Seraj E, Zarkavelis G, Petrakis D, Kollas A, Kafantari A, et al. Management of patients with recurrent/advanced cervical cancer beyond first line platinum regimens: where do we stand? A literature review. Crit Rev Oncol Hematol 2016;108:164-74. PUBMED | CROSSREF
66. Chung HC, Ros W, Delord JP, Perets R, Italiano A, Shapira-Frommer R, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol 2019;37:1470-8. PUBMED | CROSSREF
67. Naumann RW, Hollebecque A, Meyer T, Devlin MJ, Oaknin A, Kerger J, et al. Safety and efficacy of nivolumab monotherapy in recurrent or metastatic cervical, vaginal, or vulvar carcinoma: results from the phase I/II CheckMate 358 trial. J Clin Oncol 2019;37:2825-34. PUBMED | CROSSREF
68. Elit L, Fyles AW, Devries MC, Oliver TK, Fung-Kee-Fung M; Gynecology Cancer Disease Site Group. Follow-up for women after treatment for cervical cancer: a systematic review. Gynecol Oncol 2009;114:528-35. PUBMED | CROSSREF