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Review Article

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Practice guidelines for management of cervical cancer in Korea: a Korean Society of Gynecologic Oncology Consensus Statement

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ABSTRACT

Clinical practice guidelines for gynecologic cancers have been developed by academic society from several countries. Each guideline reflected their own insurance system and unique medical environment, based on the published evidence. The Korean Society of Gynecologic Oncology (KSGO) published the first edition of practice guidelines for gynecologic cancer treatment in late 2006; the second edition was released in July 2010 as an evidence-based recommendation. The Guidelines Revision Committee was established in 2015 and decided to develop the third edition of the guidelines in an advanced format based on evidence-based medicine, embracing up-to-date clinical trials and qualified Korean data. These guidelines cover strategies for diagnosis and treatment of primary and recurrent cervical cancer. The committee members and many gynecologic oncologists derived key questions through discussions, and a number of relevant scientific literature were reviewed in advance. Recommendations for each specific question were developed by the consensus conference, and they are summarized here, along with the details. The objective of these practice guidelines is to establish standard policies on issues in clinical practice related to the management in cervical cancer based on the results in published papers to date and the consensus of experts as a KSGO Consensus Statement.

Keywords: Uterine Cervical Neoplasms; Practice Guideline; Consensus; General Surgery; Chemotherapy; Irradiation

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INTRODUCTION

In 2012, cervical cancer was ranked the fourth in incidence and mortality among female cancers worldwide. Globally, cervical cancer had an estimated 528,000 new cases and was responsible for 266,000 deaths in 2012 [1]. Recently, the decreased incidence and mortality rates in developed countries have been attributed to the effectiveness of the screening test for cervical cancer. However, the incidence rate remains high in developing countries, where it accounts for 85% of all cervical cancer cases [2].

According to the Korea Central Cancer Registry data, there were 224,177 new cases of cancer in Korea in the year 2012. After excluding carcinoma in situ cases, cervical cancer was diagnosed in 3,584 cases, which comprised 1.7% of total cancer incidence, and ranking cervical cancer as the seventh most common cancer among females [3].

Although the incidence rate of cervical cancer shows a gradually decreasing trend, the incidence increased from 1993 through 2002 in women in their 20s and in those who were 70 years or older. As the incidence of cervical cancer decreased, an increase in the incidence of cervical cancer with carcinoma in situ was observed in all ages (20–80 years) [4]. This is due to early diagnosis and treatment at a precancerous stage rather than a decrease in de facto incidence of cervical cancer [2,5].

The most important risk factor for cervical cancer is the persistent high-risk human papillomavirus (HPV) infection. The rate of chronic HPV infection is approximately 10%–20% in countries with a high occurrence of cervical cancer and approximately 5%–10% [6] in countries with the low occurrence of cervical cancer. In Korea, the infection rate is reported to be approximately 10%–15%, although different results have been reported [7-10].

The test for HPV, which is a recognized cause of cervical cancer, has been recently included in the screening for cervical cancer. Additionally, the bivalent and quadrivalent HPV vaccines are being administered clinically. With effective treatments like surgery or concurrent chemoradiation therapy (CCRT), the cure rate of cervical cancer is up to 80%–90% in the early stages (stages I–II), and 60% in stage III. However, the prognosis is still poor with cancer progression to an advanced stage or recurrence.

The present guidelines are based on “The Practice Guidelines for Gynecological Cancers V2” (2010) and recent changes have been added. Key questions from clinical situation were put to thorough discussion with experts in such diverse fields as oncology, pathology, radiation oncology, radiology, and nuclear medicine. We also added an appendix with the evidence tables and the levels of evidence/recommendation.

The present practice guidelines for cervical cancer used the pathological classification (**Table 1**, modified World Health Organization [WHO] classification) recommended by the Gynecological Pathology Study Group of the Korean Society of Pathologist (GPSGKSP). There are 2 classification systems available for cervical cancer staging, the tumor, node, and metastasis (TNM) and International Federation of Gynecology and Obstetrics (FIGO) classification systems. The guidelines that used the FIGO staging were revised in early 2009 (**Table 2**).

The objective of these practice guidelines is to establish standard policies on issues in clinical practice related to the management in cervical cancer based on the results in published

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Table 1. Modified WHO histological classification of malignant tumors of the uterine cervix by the GPSGKSP

A. Epithelial tumors
· Squamous tumors
SCC
Keratinizing
Nonkeratinizing
Basaloid
Verrucous
Warty
Papillary
Lymphoepithelioma-like
Squamotransitional
Microinvasive SCC
CIN 3/SCC in situ
· Glandular tumors
Adenocarcinoma
Mucinous adenocarcinoma (Endocervical, intestinal, signet ring cell, minima deviation, villoglandular)
Endometrioid
Clear cell adenocarcinoma
Serous adenocarcinoma
Mesonephric adenocarcinoma
Early invasive adenocarcinoma
Adenocarcinoma in situ
· Other epithelial tumors
Adenosquamous carcinoma
Glassy cell carcinoma variant
Adenoid cystic carcinoma
Adenoid basal carcinoma
Neuroendocrine tumors
Undifferentiated carcinoma
B. Mesenchymal tumors
· Leiomyosarcoma
· Stromal sarcoma
· Sarcoma botryoides
· Others
C. Mixed epithelial and mesenchymal tumors
· Carcinosarcoma (MMMT)
· Adenosarcoma
D. Melanocytic tumors
E. Miscellaneous tumors
F. Lymphoid and hematopoietic tumors
G. Secondary tumors

CIN, cervical intraepithelial neoplasia; GPSGKSP, Gynecological Pathology Study Group of the Korean Society of Pathologist; MMMT, malignant müllerian mixed tumor; SCC, squamous cell carcinoma; WHO, World Health Organization.

papers to date and the consensus of experts as a KSGO Consensus Statement.

MATERIALS AND METHODS

The methods are same for those of endometrial cancer as followings [11]. The KSGO has revised the previously published practice guidelines for management of gynecologic cancer. The first edition of the practice guidelines for gynecologic cancer treatment was published in late 2006 and the second was released in July 2010 as an evidence-based recommendation. In 2015, the Guidelines Revision Committee, which was established within the KSGO, decided to produce the third edition of the guidelines. They: 1) considered the rapidly advancing developments in precision medicine and analyzed and applied the results of up-to-date

Table 2. FIGO clinical staging for uterine cervix (2008)

Stage I		The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)
IA		Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≤7 mm
	IA1	Measured stromal invasion ≤3 mm in depth and extension of ≤7 mm
	IA2	Measured stromal invasion >3 mm and not >5 mm with an extension of not >7 mm
IB		Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA*
	IB1	Clinically visible lesion ≤4 cm in greatest dimension
	IB2	Clinically visible lesion >4 cm in greatest dimension
Stage II		Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina
IIA		Without parametrial invasion
	IIA1	Clinically visible lesion ≤4 cm in greatest dimension
	IIA2	Clinically visible lesion >4 cm in greatest dimension
IIB		With obvious parametrial invasion
Stage III		The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney†
IIIA		Tumor involves lower third of the vagina, with no extension to the pelvic wall
IIIB		Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney
Stage 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 of the growth to adjacent organs
IVB		Spread to distant organs

FIGO, Fédération Internationale de Gynécologie et d'Obstétrique.

*All macroscopically visible lesions—even with superficial invasion—are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of ≤7.00 mm. The depth of invasion should not be >5.00 mm taken from the base of the epithelium of the original tissue—superficial or glandular. The depth of invasion should always be reported in mm, even in those cases with "early (minimal) stromal invasion" (–1 mm). The involvement of vascular/lymphatic spaces should not change the stage allotment. †On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause.

clinical trials, including target therapies; 2) accepted and included the recently revised World Health Organization histological classification; and 3) applied, as evidence, the data obtained from a number of Korean studies of gynecologic cancer surgery.

These guidelines were designed according to the principles of evidence-based medicine, which is the international standard method for building clinical practice guidelines. These guidelines went through a process of 1) selecting key questions; 2) searching for evidence; 3) evaluating the level of evidence and determining the grade of recommendation; 4) deduction of the agreements; and 5) review and approval. Key questions were selected through discussion among the members of the cervical cancer team after analysis of previous recommendations, consensus for revision, and confirmation of the recent significant reports (**Supplementary**). Data and literature published before 2015 in Korea and other countries were searched using Cochrane Library CENTRAL, MEDLINE, and EMBASE, and then a meta-analysis and systematic literature review were conducted. The collected evidence was evaluated for quality using Cochrane methodology for randomized controlled trials, the Newcastle-Ottawa scale for nonrandom studies, and the quality assessment of studies of diagnostic accuracy included in systematic reviews (QUADAS-2) for diagnosis research. The level of evidence was divided into 4 categories using the methodology suggested by the Grade Group based on the research design, consistency among the research results, immediacy of the research subject and intervention, possibility of publishing bias, and accuracy of the research results (**Table 3**). The grade of recommendation was decided by the methodology suggested by the grade group based on the level of evidence, considering the application subject, hazard and benefit, social and individual cost of the intervention, and patients' preference. The grades of recommendation were divided into strong recommendation and weak recommendation. The draft form and grades of recommendation were established through consultation that included all members of the revision committee.

Table 3. Levels of evidence and grades of recommendation

	Grade and recommendation strength
Levels of evidence	
A	High-quality evidence
B	Moderate-quality evidence
C	Low-quality evidence
D	Very low-quality evidence
E	No evidence or difficult to analyze
Grade and recommendation strength	
1	Strong recommendation
2	Weak recommendation

After debates in a public hearing with all members of the KSGO and invited representatives of related academies, a draft version of the guidelines was evaluated and supplemented. For an internal and external review, the KSGO sent the final version of the guidelines to related organizations, including the Korean Society for Radiation Oncology (KOSRO), Korean Society of Pathologists (KSP), Korean Cancer Study Group (KCSG), Korean Society of Urogenital Radiology (KSUR), Korean Society of Nuclear Medicine (KSNM), Korean Society of Obstetrics and Gynecology (KSOG), and Korean Gynecologic Oncology Group (KGOG). Subsequent to these reviews, there were no objections or requests for revision.

The histopathological classification recommended by the GPSGKSPs was used as the histopathological classification of these guidelines on cervical cancer. Regarding the staging system of cervical cancer, the FIGO stage classification was applied in these revised guidelines.

CLINICAL CONSIDERATIONS AND RECOMMENDATIONS

1. Diagnosis

Cervical cancer is usually asymptomatic in the early stages, and later may be accompanied by an increase in vaginal discharge, bleeding after sexual intercourse, and intermittent spotty bleeding. Cytology and HPV test can be used for screening for cervical cancer, and colposcopy-guided biopsy is used to accurately make a diagnosis. Cervical conization is recommended to determine the depth of infiltration or microscopic infiltration. In FIGO stage IA, the tumor is latent and invisible to bare eyes. Stage IA1 is defined as stromal infiltration that is less than or equal to 3.0 mm, and stage IA2 is defined as stromal infiltration that is greater than 3.0 mm and less than or equal to 5.0 mm. In both stages IA1 and IA2, the horizontal spread of tumor should be less than or equal to 7.0 mm. These diagnoses must be made with cervical conization. Following the pathologic diagnosis of cervical cancer, basic tests are performed such as blood tests (complete blood count, the biochemical analysis including tests for liver and kidney functions), urine test, chest X-rays, and echocardiography.

Imaging tests can be performed in addition to colposcopy, punch biopsy, cervical conization, cystoscopy, and colonoscopy, which FIGO currently presents as methods for determining the stage of cervical cancer. Although imaging tests like computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), PET/CT (1C) or surgical staging are not included in the methods that FIGO acknowledges for the staging of cervical cancer, these can be selectively performed in order to decide the direction of treatment [12-14]. Cystoscopy and colonoscopy are performed for stage IB2 or higher lesions, particularly when invasive cancer to the bladder or colon is suspected.

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The squamous cell carcinoma (SCC) antigen, a tumor marker, is a useful serologic marker for SCC. The SCC antigen level prior to treatment is related to cancer stage, tumor size, depth of infiltration in the cervix, presence or absence of infiltration in the lymphovascular space, presence or absence of lymph node metastasis, and clinical results. Thus, tumor markers such as SCC antigen can be measured before treatment and during follow-up [15].

KQ 01. Are PET/ CT scans more sensitive than the CT or MRI in predicting lymph node metastasis for the treatment of cervical cancer?

There is insufficient evidence that PET/CT is more sensitive than CT or MRI to predict pelvic or para-aortic lymph node metastasis. PET/CT shows discrepant results in terms of sensititivity in selected studies for meta-analysis. As per the study protocol, CT, MRI, and PET/CT have different sensitivity, specificity, negative predictive value and positive predictive value [12,13]. Overall, when metastases are not identified in the CT or MRI scans or when the results are uncertain, PET/CT could be helpful in predicting pelvic or aortic lymph node metastasis.

Recommendation: PET/CT could be performed prior to the treatment for cervical cancer.
Level of evidence: C (low).
Strength of recommendation: 1 (strong).

2. Treatment

The primary treatment of early stage cervical cancer is either surgery or radiation therapy after clinical staging work-up. Conization or simple hysterectomy (1B) is the primary treatment for stage IA1 disease [16]. For stage IA1 patients with no evidence of involved resection margin and lymphovascular space invasion (LVSI) after conization, observation is an option for selected patients who desire fertility preservation. In stage IA1 with involved resection margin or LVSI after conization, options include repeat-conization with negative margin, simple hysterectomy or type II radical hysterectomy in addition to pelvic lymphadenectomy (2D) [17-19]. For stage IA1 patients with LVSI who desire to preserve fertility, radical trachelectomy with pelvic lymphadenectomy is recommended. Conization or simple trachelectomy is a reasonable option (2D).

Radical hysterectomy with pelvic lymph node dissection is preferred for patients with stage IA2 cervical cancer. Pelvic radiation therapy is a treatment option for patients who are medically inoperable or depending on clinician's discretion. For patients with stage IA2–IB1 disease who desire fertility preservation, radical trachelectomy, and pelvic lymph node dissection is recommended [20,21]. Minimally invasive surgical approaches such as laparoscopic or robotic surgery are recommended for treatment (1D). For a patient with early staged cervical cancer, nerve-sparing radical hysterectomy is an option (2C). In addition, less radical surgery like type 1 hysterectomy may offer a treatment option for carefully selected patients with lesions less than 2 cm in diameter that have no parametrial and nodal involvement (2D) [22,23].

Radical hysterectomy plus pelvic lymph node dissection with or without para-aortic lymph node sampling is typically reserved for patients with stage IB1 or IIA1. For patients who desire fertility preservation, radical trachelectomy and pelvic lymph node dissection could be an option for selected cases with early stage disease. Adjuvant pelvic radiation therapy is recommended after radical hysterectomy in patients who have at least 2 of the following intermediate risk factors: cervical tumor diameter of more than 4 cm, greater than two-

third stromal invasion, and LVSI. The role of CCRT in these patients group is currently being evaluated in an international phase III randomized trial (GOG 263, NCT01101451, www.gog.org). Adjuvant CCRT is indicated for patients with high-risk factors (positive resection margins, positive lymph nodes, parametrial extension) who underwent the radical hysterectomy and pelvic lymphadenectomy [24]. In the case of radical hysterectomy with therapeutic lymph node dissection, chemotherapy alone or observation with omitting radiotherapy could be one of the options even with high-risk-factors [25] .

For patients with stage IB2–IIA2 disease, concurrent cisplatin-containing CCRT is recommended [26,27]. In patients treated with CCRT, adjuvant hysterectomy may be considered depending on clinical situation. For patients with stage IB2–IIA2 disease, radical hysterectomy followed by tailored adjuvant treatment (radiation or CCRT) is an option because this strategy shows comparable survival outcomes to primary CCRT (2C). In retrospective data on patients with stage IB2–IIA2 cervical cancer, neoadjuvant chemotherapy may show equal or prolonged 5-year overall survival compared to radiation therapy or surgery alone [26,28,29]. However, the role of neoadjuvant chemotherapy in these patients group is deferred until the analysis of current European Organization for Research and Treatment of Cancer (EORTC) phase III randomized trial is completed (http://groups.eortc.be/gcg/studyprotocols.htm).

It is essential to evaluate the involvement of para-aortic lymph nodes in planning treatment strategies for patients with stage IIB to IVA disease. Surgical staging like extraperitoneal or laparoscopic lymph node dissection is the most accurate modality to evaluate the nodal involvement, and therefore should be considered. Radiologic imaging studies including CT/MRI/PET-CT could be one of the options to evaluate the lymph node status based on the institutional environments (1C) [30]. These patients with no evidence of para-aortic nodal involvement are treated with pelvic radiation plus concurrent cisplatin based-chemotherapy [27]. Those with para-aortic nodal involvement could be treated with extended field radiation plus concurrent chemotherapy. However, systemic chemotherapy and individualized radiation therapy could be considered depending on the physician's discretion and the clinical situations. For patients who present with stage IVB, systemic chemotherapy and individualized radiation therapy are recommended (1B).

The methodology of radiation therapy recommended by this KGOG guideline are as follows. With the use of 3D imaging, 3D conformal radiation therapy plans are designed to adequately cover soft tissue regions at risk and minimize the dose to the bowel and other normal structures. Intensity-modulated radiation therapy (IMRT) may be helpful in minimizing the dose to the normal structures and delivering high dose to regions at risk. IMRT could be used as primary therapy since this modality resulted in similar survival and less gastrointestinal and urologic toxicity compared with conventional radiation therapy (2C). When tumor involves the lower third of the vagina, irradiation of inguinal lymph nodes is needed. Intracavitary brachytherapy is an essential component of treatment for cervical cancer and interstitial brachytherapy is a critical component for treatment of cervical cancer with parametrial invasion, especially for stage IIIB or more disease.

It is necessary to minimize the radiation dose to the bladder, rectum, colon and other normal structures. The coned-down shaped field may be considered in patients with gross disease in the parametria or unresected nodes. With the use of individualized central blocking techniques, it can be minimized to exposure to small intestine, rectum and bladder that are irradiated from intracavitary brachytherapy. It is recommended that total duration of

radiation therapy treatment should be completed within 8 weeks. Once after initiation of radiation therapy, it should be avoided to delay or split the radiation therapy.

Five randomized clinical trials have shown that the use of CCRT results in a significantly improved overall survival in patients with locally advanced cervical cancer compared with radiation therapy alone [31]. Therefore, CCRT is the first line treatment for patients with locally advanced cervical cancer. Concurrent chemotherapeutic regimens include weekly cisplatin or the combination of cisplatin and 5-fluorouracil (5-FU) every 3 to 4 weeks. Concurrent paclitaxel-based CCRT can be considered based on the recent data [32-35]. Further researches are needed regarding the optimal radiation field. In patients with confirmed or suspicious para-aortic node involvement, extended field radiation therapy is recommended. Adjuvant chemotherapy following definitive CCRT is not recommended in patients with locally advanced cervical cancer since there is a lack of data supporting the benefit of consolidation chemotherapy (2C).

There are insufficient data regarding the treatment guideline for patients with incidental cervical cancer after simple hysterectomy. Work-up for these patients include history taking, physical examination, and imaging such as CT, MRI, and/or PET/CT. For patients with stage IB2 or more disease, cystoscopy and rectoscopy may be performed. For patients with pathologically proven stage IA1 disease, observation is recommended. For patients with stage IA1 with LVSI and these with stage IA2, further treatment strategy is based on the surgical margin status and the imaging work-up. If the positive surgical margin and no lymph node from image study, CCRT including indivualized brachtherapy is recommended. If the patients with stage IA2 or more disease have negative surgical margin and no nodal involvement on the imaging, options include as follows [36]: 1) external beam radiation therapy with or without brachytherapy with concurrent cisplatin-based chemotherapy; and 2) parametrectomy and lymphadenectomy. If the surgical marign is involved or residual disease/nodal involvement is found on the imaging, CCRT including brachytherapy. In a case of positive parametrial resection margin or nodal involvement after parametrectomy and lymphadenectomy, adjuvant CCRT is recommended.

KQ 02. Does laparoscopic or robotic surgery have similar survival outcomes compared to open surgery for radical hysterectomy in cervical cancer stage IB–IIA?

There is no randomized trial comparing laparoscopic or robotic surgery and open surgery. Based on the meta-analysis, relative risk reduction (RRR)=27%, event rate (ER)=7.4%, optimal information size (OIS)=600, and the number of death=50 is needed to have statistically significant results. This means that larger number of the study population is needed to clarify the differentiation in the death. From several retrospective studies, treatment outcome in terms of progression-free and overall survival is comparable between 2 groups [37-40].

Recommendation: Laparoscopic or robotic radical hysterectomy can be performed in cervical cancer stage IB–IIA.
Level of evidence: D (very low).
Strength of recommendation: 1 (strong).

KQ 03. Does the nerve sparing radical hysterectomy have similar survival outcome compared to type III hysterectomy in early staged cervical cancer?

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Meta-analysis was reported investigating the survival outcome in early cervical cancer. In early cervical cancer, survival outcome after nerve sparing radical hysterectomy is similar to that of type III hysterectomy and results in decreased urinary difficulty. Based on the meta-analysis, RRR=39%, ER=6.8%, OIS=200, and the number of death=5 is needed to have statistical analysis. One randomized trial and one non-randomized trial showed no impact of nerve sparing radical hysterectomy on survival outcome [41,42].

Recommendation: Nerve sparing radical hysterectomy could be performed in early staged cervical cancer.
Level of evidence: C (low).
Strength of recommendation: 2 (weak).

KQ 04. Can we have similar survival outcome with type I hysterectomy compared to radical hysterectomy in women with cervical cancer ≤2 cm?

Although based on the limited study results including one prospective randomized trial, we do not observe the definitive loss of survival outcome from type I hysterectomy compared to radical hysterectomy in women with cervical cancer ≤2 cm and type I hysterectomy shows better outcome for complication [43]. RRR=62%, ER=26%, OIS=100, and the number of death=22 is needed for the near future prospective study.

Recommendation: Type I hysterectomy might be performed in a case of higher estimation of postoperative complication based on the clinical decision.
Level of evidence: D (very low).
Strength of recommendation: 2 (weak).

KQ 05. Does IMRT result in less complications compared to standard radiotherapy in women with cervical cancer?

Three non-randomized prospective studies support primary use of IMRT for cervical cancer [44-46]. Toxicity has been reduced with similar survival outcomes. However, there is risk of bias related randomization and allocation concealment for the previous results. RRR=83%, ER=50%, OIS=50, and the number of death=7 is needed for the near future prospective study.

Recommendation: IMRT could be used as primary treatment for cervical cancer, based on the similar treatment outcome in terms of recurrence and survival with fewer complication rate.
Level of evidence: C (low).
Strength of recommendation: 2 (weak).

KQ 06. Does radical hysterectomy result in similar survival outcome like concurrent chemoradiotherapy in cervical cancer stage IB2 and IIA2?

Similar survival outcome has been observed between radical hysterectomy with selective adjuvant treatment and primary concurrent chemoradiotherapy in cervical cancer stage IB2 and IIA2 [25,47-50]. Althought the result of one randomized trial is not consistent to that of 4 non-randomized study, decrease of survival has not been observed in primary surgical group.

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Recommendation: Radical hysterectomy and concurrent chemoradiotherapy could be selectively used considering the clinical situation of patients.
Level of evidence: C (low).
Strength of recommendation: 2 (weak).

KQ 07. Does simple trachelectomy or conization have similar survival outcome with radical hysterectomy in cervical cancer stage IA1 with lymphovascular space invasion?

From the 2 comparison studies and 2 non-comparison studies, similar survival outcomes have been identified in total 61 patients [17,51-53].

Recommendation: Simple trachelectomy and conization could be performed for women with cervical cancer IA1 with lymphovascular space invasion, based on the similar survival outcomes from the radical hysterectomy.
Level of evidence: D (very low).
Strength of recommendation: 2 (weak).

KQ 08. Does addition of adjuvant chemotherapy after concurrent chemoradiotherapy improve survivals in patients with locally advanced cervical cancer?

Although statistical heterogeneity is not significant (I^2=23%) from the 2 randomized trials, estimated direction of effect is the opposite each other. Addition of adjuvant chemotherapy after concurrent chemoradiotherapy in patients with locally advanced cervical cancer has not been supported from the previous studies [54].

Recommendation: The addition of adjuvant chemotherapy after concurrent chemoradiotherapy has not been recommended.
Level of evidence: C (low).
Strength of recommendation: 2 (weak).

3. Surveillance

The basic principle for patient's surveillance after treatment is every 3–4 months for initial 2 years and every 6 months following 3 years. The surveillance strategies should be modified based on the patietns' clinical situation and the environment. History taking and physical examination including pelvic examination might be considered. PAP smear might be examed at least every year. PAP smear, laboratory test, image tests such as chest X-ray, CT, MRI, PET/CT, or tumor marker could be tested based on the clinical decision [55]. PET/CT is helpful to identify a metastasis with the conventional image or to confirm the extent of recurrence (1C). Use of dilator is recommended for sexually active women after radiation therapy to preserve sexual function and evaluate the cervix efficiently with PAP smear.

4. Treatment for recurrence

Recurrence of cervical cancer could be identified with image study; invasive procedures are selectively used to confirm the recurrences.

1) Recurrence in the pelvis or local recurrence

In a case of naïve radiation therapy, CCRT should be considered, with selective use of brachytherapy [56]. Pelvic exenteration might be selectively considered in the case of the previous radiation therapy in the pelvis [57]. Re-administration of radiation therapy might be selectively used [58-60].

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2) Extra-pelvic recurrence

Chemotherapy or palliative care could be considered in the case of extra-pelvic recurrence, para-aortic lymph node recurrence, multiple metastases, or surgically unresectable metastasis. Chemotherapy, surgical resection, radiation therapy or CCRT could be considered in the case of isolated recurrence [61,62].

Salvage chemotherapy could be considered in women with recurrent cervical cancer who does not candidates for radiation therapy or pelvic exenteration. Cisplatin-doublet is recommended for recurrent or metastatic cervical cancer patients as the first line treatment, and single cisplatin (50 mg/m^2 q 3 weeks) could be used in case of unavailable of cisplatin-double.

Paclitaxel is recommended as the combination drug with cisplatin, and other suggested drugs are topotecan and gemcitabine. The current guideline recommended the chemotherapeutic agents like in **Table 4**. The suggested drug as the second line treatment for recurrent and metastatic cervical cancer is bevacizumab [35], ifosfamide [57], topotecan [61], irinotecan [62-64], mitomycin [63], gemcitabine [65], and 5-fluorouracil [66,67]. Addtion of bevacizumab decrease the mortality 29% (1B). Comprehensive approaches including palliative and supportive care are needed for intractable cervical cancer.

KQ 09. Does PET/CT improve the accuracy of diagnosis of recurrence compared to CT or MRI in cervical cancer?

Statistical analysis for the diagnostic accuracy of CT, MRI, and PET/CT has not been performed due to heterogeneity of the statistical analysis from each studie [68-71]. From the review of each study, PET/CT could be used to identify the recurrence of cervical cancer when recurrence is not identified or recurrence is suspicious with conventional image. And PET/CT might be used to confirm the field of recurrence.

Recommendation: PET/CT could be performed clinically if diagnosis of recurrent cervical cancer with CT/MRI is uncertain or PET/CT is needed to confirm the field of recurrence.
Level of evidence: C (low).
Strength of recommendation: 1 (strong).

KQ 10. Does addition of bevacizumab to conventional chemotherapy improve survival in patients with recurrent or persistent cervical cancer?

Table 4. Chemotherapeutic agent used for recurrent or metastatic cervical cancer

First line therapy
Cisplatin+paclitaxel+bevacizumab
Cisplatin+paclitaxel
Cisplatin+topotecan+bevacizumab
Cisplatin+topotecan
Cisplatin (preferred as a single agent)
Cisplatin+vinorelbine
Cisplatin+gemcitabine
Cisplatin+isocyanide
Carboplatin+paclitaxel
Carboplatin
Paclitaxel

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One randomized trial suggests that addtion of bevacizumab improve survival outcome (HR, 0.29) [72].

Recommendation: Bevacizumab could be used for recurrent or persistent cervical cancer to improve survival outcomes.
Level of evidence: B (moderate).
Strength of recommendation: 1 (strong).

SUMMARY OF RECOMMENDATION AND CONCLUSIONS

The following recommendations and conclusions are based on 4 levels of evidence (A, high; B, moderate; C, low; D, very low) and 2 strengths of recommendation (1, strong; 2, weak).

1. There is insufficient evidence that PET/CT is more sensitive than CT or MRI to predict pelvic or para-aortic lymph node metastasis. However, when metastases are not identified in the CT or MRI scans or when the results are uncertain, PET/CT could be helpful in predicting pelvic or aortic lymph node metastasis. Thus, PET/CT could be performed prior to the treatment for cervical cancer **(1C)**.

2. Treatment outcome in terms of progression-free and overall survival is comparable between 2 groups. Based on the results, laparoscopic or robotic radical hysterectomy can be performed in cervical cancer stage IB–IIA **(1D)**.

3. In early cervical cancer, survival outcome after nerve sparing radical hysterectomy is similar to that of type III hysterectomy and results in decreased urinary difficulty. Therefore, nerve sparing radical hysterectomy could be performed in early staged cervical cancer **(2C)**.

4. Although based on the limited study results, we do not observe the definitive loss of survival outcome from type I hysterectomy compared to radical hysterectomy in women with cervical cancer ≤2 cm and type I hysterectomy shows better outcome for complication. For these reasons, type I hysterectomy might be performed in a case of higher estimation of postoperative complication based on the clinical decision **(2D)**.

5. IMRT could be used as primary treatment for cervical cancer, based on the similar treatment outcome in terms of recurrence and survival with fewer complication rate **(2C)**.

6. Similar survival outcome has been observed between radical hysterectomy and concurrent chemoradiotherapy in cervical cancer stage IB2 and IIA2. Therefore, 2 treatment options could be selectively used considering the clinical situation of patients **(1C)**.

7. Simple trachelectomy and conization could be performed for women with cervical cancer IA1 with lymphovascular space invasion, based on the similar survival outcomes from the radical hysterectomy **(2D)**.

8. The addition of adjuvant chemotherapy has not been recommended as the standard treatment after concurrent chemoradiotherapy in patients with locally advanced cervical cancer because of unavailable evidence to support it **(2C)**.

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9. Statistical analysis for the diagnostic accuracy of CT, MRI and PET/CT has not been performed due to heterogeneity of the study performance. PET/CT could be performed clinically if diagnosis of recurrent cervical cancer with CT/MRI is uncertain or PET/CT is needed to confirm the field of recurrence **(1C)**.

10. Bevacizumab could be used for recurrent or persistent cervical cancer to improve survival outcomes **(1B)**.

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SUPPLEMENTARY MATERIAL

Supplementary

Guideline development process in accordance with the evidence-based medicine

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