CANCER OF THE UTERINE CERVIX

Effective Date: September 2015

The recommendations contained in this guideline are a consensus of the Alberta Provincial Gynecologic Oncology Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

Cancer of the uterine cervix is the third most common cancer of the female genital tract (twelfth most common cancer overall, among women). It accounts for 1.6% of all cancers in women and is the sixteenth leading cause of death due to all cancers in women. [1] In Alberta, there were 135 new cases and 35 deaths in 2012.[2] The five-year survival rate for cervical cancer is about 71%, as most cases are detected early due to the use of Pap tests.[3] Most cases are found in women under the age of 50 years.[4]

There are several histological types of cervical cancer. These include squamous cell (epidermoid) carcinoma, adenocarcinoma, adenosquamous carcinoma, small cell carcinomas, and primary sarcomas of the cervix. Staging of cervical cancer is based on the Federation Internationale de Gynecologie et d'Obstetrique (FIGO).[5] The classification system was updated in 2010.[6] A detailed description of this staging system can be found in the Appendix.

GUIDELINE QUESTIONS

- What should be considered during the staging of patients so that the appropriate primary treatment is given?
- Does radiotherapy following surgery, versus surgery alone, increase survival rates among patients with early stage disease?
- What are the appropriate indications for adjuvant therapy either after primary surgery or radiotherapy?
- Is chemoradiotherapy more effective than radiotherapy alone in increasing survival? If so, what is the optimal platinum-containing chemotherapy regimen?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Gynecologic Oncology Tumour Team. Members of the Alberta Provincial Gynecologic Oncology Tumour Team include gynecologic oncologists, radiation oncologists, medical oncologists, pathologists, nurses, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gynecologic Oncology Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in April 2009. This guideline was revised in 2011, 2012, 2013 and 2015.

SEARCH STRATEGY

Entries to the Medline, EMBASE, and Cochrane databases and clinical practice guideline databases were searched for evidence relevant to this topic. Search terms included: *cervix* or *cervical* or *uterine cervix* AND *carcinoma* or *neoplasm* or *cancer*, with limits of human studies only. Among the studies returned by

the search, those that did not report survival or toxicity outcomes and those that had fewer than 100 patients per treatment arm were excluded.

Guidelines reviewed include the following: the National Comprehensive Cancer Network (NCCN) guidelines,[7] the European Society for Medical Oncology (ESMO) guidelines,[8] the BC Cancer Agency (BCCA) guidelines,[9] and Cancer Care Ontario (CCO) Program in Evidence-Based Care guidelines,[10-12] the Tom Baker Cancer Centre,[13] and the American Society of Clinical Oncology (ASCO).[14] An effort was made to either adapt or adopt the most appropriate guidelines from other sources so that work wasn't duplicated. An evidence based perspective was used to draft proposals. Where evidence was weak a guideline was developed using pragmatic consensus within the group.

The guideline was originally developed in 2009 and then updated in 2011, 2012, 2013, and again in 2015. The literature was reviewed prior to each update, using the search strategy described above. The 2012 and 2013 reviews included a total of 21 studies and 2 studies, respectively. The 2015 review focused on neoadjuvant chemotherapy, upfront lymph node debulking, sentinel lymph node biopsy (SLNB) and trachelectomy and included a total of 21 studies. Following a review of the evidence by the Alberta Gynecologic Oncology Team, relevant literature was added to the discussion section.

TARGET POPULATION

The recommendations outlined in this guideline apply to adults over the age of 18 years with cancer of the uterine cervix, including squamous, adenocarcinomas, and adenosquamous carcinomas. Rare histologies will be treated on an individual basis.

RECOMMENDATIONS

I. Staging

Investigations may include
- History and clinical examination
- Cervical biopsy; an expert pathology review should be performed by a pathologist with experience in gynecologic pathology.
- Blood work (CBC, LFT, renal function studies)
- Imaging is optional for stage <IB1. For stage IB1 and higher, MRI is recommended; chest x-ray and PET-CT may be performed.
- Cone biopsy, as indicated

II. Treatment

Consider enrollment in a clinical trial, if available. Up to date information on trials offered in Alberta is available on the Alberta Cancer Clinical Trials website.

FIGO Stage IA1
Preferred options include:
- Conization with free margins
- OR simple hysterectomy
- OR modified radical hysterectomy if there is multifocal invasion

- If there is lymphovascular space involvement, consider pelvic lymphadenectomy

FIGO Stage IA2
Preferred options include:
- Conization +/- pelvic lymphadenectomy (PLND) +/- para-aortic lymphadenectomy (PALND) +/- sentinel lymph node biopsy (SLNB)
- OR simple or modified radical hysterectomy +/- PLND +/- PALND +/- SLNB
- OR radical or simple trachelectomy for fertility preservation +/- PLND +/- PALND +/- SLNB

Special Considerations
Radical or simple trachelectomy indications:
- Lesion ≤ 2 cm
- Preservation of fertility
- Small adenocarcinomas can be considered at physician discretion
- No lymphovascular invasion; limited endocervical involvement

SLNB indications:
- SLNB is recommended when performed at a centre with a validated technique

FIGO Stage IB1
Preferred options include:
- Radical hysterectomy + PLND +/- PALND +/- SLNB; adjuvant post-operative radiotherapy is considered only when adverse pathological findings are found
- OR pelvic RT + brachytherapy. This is usually considered for patients who are not candidates for surgery; although less evidence is available to support the addition of chemotherapy to primary RT for this subgroup, chemoradiation is the preferred option.
- OR radical or simple trachelectomy + PLND +/- PALND +/- SLNB could be considered for patients wishing fertility preservation

Post-operative adjuvant therapy guidelines as described below will be applied to this subgroup.

FIGO Stage IB2
Preferred options include:
- Pelvic RT + concurrent chemotherapy (cisplatin × 5 - 6 cycles) followed by brachytherapy. There is insufficient evidence to recommend upfront lymph node debulking.
- OR radical hysterectomy + PLND +/- PALND

Neoadjuvant chemotherapy can be considered for this subgroup, but there is a lack of high quality evidence to support this as the standard of care.

Post-operative adjuvant therapy guidelines as described below will be applied to this subgroup.

FIGO Stage IIA1
Preferred options include:
- Pelvic RT + concurrent chemotherapy (cisplatin × 5 - 6 cycles) followed by brachytherapy
- OR radical hysterectomy + PLND +/- PALND *in selected circumstances*

Neoadjuvant chemotherapy can be considered for this subgroup, but there is a lack of high quality evidence to support this as the standard of care.

Post-operative adjuvant therapy guidelines as described below will be applied to this subgroup.

FIGO Stage IIA2
Preferred options include:
- Pelvic RT + concurrent chemotherapy (cisplatin × 5 - 6 cycles) followed by brachytherapy. There is insufficient evidence to recommend upfront lymph node debulking.
- OR radical hysterectomy + PLND +/- PALND *in selected circumstances*

Neoadjuvant chemotherapy can be considered for this subgroup, but there is a lack of high quality evidence to support this as the standard of care.

Post-operative adjuvant therapy guidelines as described below will be applied to this subgroup.

FIGO Stage IIB/IIIA/B/IV
Options include:
- Medically fit patients: tailored EBRT + concurrent chemotherapy (cisplatin × 5-6 cycles) followed by brachytherapy, there is insufficient evidence to recommend upfront lymph node debulking
- Medically unfit patients: palliative or radical RT can be given at the discretion of the radiation oncologist

<u>Post-operative Adjuvant Therapy</u>
Consider the following risk factors when deciding on appropriate treatment options:
- Histology (e.g. adenocarcinoma, adenosquamous versus squamous cell carcinoma)
- Tumour size
- Depth of stromal invasion
- Lymphovascular space invasion (LVSI)
- Nodal status
- Parametrial margin status
- Vaginal margin status

<u>Radiation Therapy</u>
Radiation therapy should be administered as follows:
Pelvic RT: 45 – 50.4 Gy in 25 – 28 fractions (1.8 to 2.0 Gy per fraction) over 5-5.5 weeks
- Intracavitary brachytherapy may include HDR or PDR techniques
- Boost to the parametria may be given as clinically indicated.

Note: Patients should maintain adequate hemoglobin level during radiotherapy.

<u>Special Clinical Scenarios</u>
- Adjuvant hysterectomy may be considered among patients in whom intracavitary insertion is unsuccessful after the initial chemoradiation, and the patient is unable to have brachytherapy. [15]
- If intracavitary brachytherapy cannot be performed, and patient is not a surgical candidate, consider a smaller pelvic boost technique (e.g. 3D conformal or IMRT may be considered). [16]

Adjuvant Chemotherapy
Cisplatin should be administered at a radiosensitizing dose of 40 mg/m^2 (max = 80) intravenously over one hour weekly for 5 - 6 cycles during EBRT.[17]

Recurrent/Persistent Disease

Investigations may include
- History and clinical examination
- Blood work (CBC, LFT, renal function studies)
- Imaging: chest x-ray; CT-PET chest, abdomen and pelvis, MRI of the pelvis

Treatment options for *curable* pelvic recurrence include:
- Radical RT, with or without cisplatin, for patients previously treated with surgery
- Pelvic exenteration, for patients previously treated with upfront radical RT

Treatment for *incurable* pelvic recurrence may include palliative RT and chemotherapy.

Treatment options for extra-pelvic recurrences include:
- Clinical trial
- Palliative chemotherapy
- Palliative RT

III. Follow Up and Surveillance

The following recommendations have been modified from the Cancer Care Ontario[12] follow-up guidelines:
- Inform patients about symptoms of recurrence.
- For the first two years, patients should be followed closely by a physician experienced in the surveillance of cancer patients; follow-up visits should be held every 3 to 4 months within the first two years.
- After the first two years, the patient can be discharged to the primary care physician; follow-up visits should be held annually and should include annual cytology.
- Follow-up visits should include a history (e.g. any symptoms elicited) and complete physical examination (including a speculum exam with bimanual and pelvic/rectal examination).
- There is little evidence to suggest that vaginal vault cytology more than once a year is useful.

DISCUSSION

Primary Therapy

Early stage cervical cancer is usually treated with either surgery or radiotherapy alone depending on age and other patient factors. Adjuvant postoperative radiotherapy is considered only when adverse pathological findings are found. Observation may be an option for select stage IA1 patients, if fertility is to be preserved.[8] Surgery alone is generally reserved for stage IA1, IA2, and IB1 patients.[13,18] Surgical procedures include cone biopsy, trachelectomy or simple or modified radical hysterectomy, with or without pelvic lymphadenectomy. Pelvic lymphadenectomy should be mainly used in stage IB disease or higher, as lymph node metastases occurs in only 0.5% of stage IA2 patients.[19] Radical or simple trachelectomy

may be used for stage IB1 if the lesion is < 2 cm, there is no lymphovascular space invasion, and preservation of fertility is desired. In a randomized controlled trial setting, preoperative intracavity high dose rate brachytherapy (HDR-BT; 2x8 Gy) plus radical surgery was compared with no preoperative treatment plus radical surgery in operable FIGO stage IA2-IIB patients; the pathological complete response rate was significantly higher (26.8% [11/41] vs. 7.1% [3/42]; p = 0.0204) in the preoperative BT group.[20]

Medically fit patients with advanced stage cervical cancer (stage IB2/IIB/IIIA/IIIB/IVA), as well as select stage IIA cases, should be considered for treatment with concurrent radiotherapy and chemotherapy.[8,10,13,18] A meta-analysis of 13 trials showed that chemoradiotherapy (versus radiotherapy alone) increased the disease free survival rate at five years by eight percent.[17] There was a significant trend towards increased overall survival with decreasing stage of disease (p = 0.017), with stage IA/IB/IIA patients achieving the lowest hazard ratio for death. In 1999 a clinical alert was communicated supporting the use of concurrent chemotherapy in locally advanced cervix cancer patients. One of the trials forming this alert had included PA node radiation as part of its control arm. Given that the chemotherapy experimental arm achieved superior survival it is recommended that routine PA node radiotherapy no longer be applied to this subgroup of patients. Medically unfit patients may be treated with palliative radiotherapy given at the discretion of the radiation oncologist.[18] For distant metastases, systemic therapy or individualized radiotherapy could be offered.

Radiation therapy should be administered as 45 – 50.4 Gy in 25 – 28 fractions (1.8 - 2.0 Gy per fraction) over five to five and a half weeks. The addition of intracavitary brachytherapy may include HDR or PDR techniques. A boost to the parametria can be given (usually 1.8 to 2.0 Gy per fraction) over three to five fractions, as clinically indicated. If brachytherapy is technically not feasible, then an external beam boost can be given using conformal radiotherapy or intensity modulated radiotherapy. For patients in whom intracavitary insertion is unsuccessful after the initial treatment with chemoradiation, an adjuvant hysterectomy may be considered. A recent retrospective analysis showed that, in this setting, adjuvant hysterectomy (versus further pelvic external beam radiotherapy) was associated with a nonsignificant decrease in the rate of relapse (0 patients, 0% vs. 7 patients, 50%; p=0.068) and the rate of death from recurrent disease (0 patients, 0% vs. 6 patients, 43%; p = 0.152) after 63 months of follow up.[15] Radio-therapy to the PA lymph nodes is also suggested if there is known to be radiological or identified pathologic involvement of the common iliac chain or PA nodes. Such treatment can be delivered synchronously with the pelvic RT, but where patients are receiving cisplatin based chemotherapy it will likely be necessary to delay the PA lymph node treatment until after the pelvic treatment. There is minimal evidence to drive practice in this area.

The optimal regimen for concurrent chemoradiation has not yet been defined; however, cisplatin-based concurrent chemoradiation has been used in several trials,[21-23] including three Gynecologic Oncology Group Trials,[24-26] that showed a significant benefit of chemoradiation versus radiotherapy alone. The most common regimen used in these trials was cisplatin at a dose of 40 mg/m^2 intravenously over one hour weekly for five to six cycles.

Upfront lymph node debulking has been proposed for patients with locally advanced stage cervical cancer to improve treatment planning and possible therapeutic benefit. However, there is insufficient evidence to recommend this procedure. A Cochrane review identified one trial investigating pretreatment lymph node dissection for surgical staging and was therefore unable to provide specific conclusions on the effectiveness of this treatment and recommended individualized treatment.[27]

There is growing evidence for the use of sentinel lymph node biopsy (SLNB) for nodal staging in patients with early stage cervical cancer. Nodal stage is an important predictor of prognosis that can be used to guide treatment decisions.[28,29] Furthermore, SLNB may reduce the need for a lymphadenectomy, which is associated with complications such as lymphedema.[30] The feasibility of this procedure is demonstrated by a 2013 meta-analysis that included 17 studies with 1112 patients receiving SLNB.[31] The authors reported a pooled detection rate of 92.2%, sensitivity of 88.8%, negative predictive value of 95% and the results improved when limited to tumours ≤ 2 cm. An additional meta-analysis including 67 studies conducted in 2014 found similar results; a pooled sentinel node detection rate of 89.2% and sensitivity of 90%.[32] In particular, the SENTICOL multicenter prospective study (n = 139 with stage IA1 or IB1 cervical cancer) found SLNB (with intracervical injection of radiocolloid and blue dye) is able to detect unusual drainage pathways and micrometastases resulting in improved nodal staging; detection rate of 97.8%, sensitivity of 92% and two false-negative results.[33] Although research shows the value of SLNB there is currently no standard protocol for conducting the procedure. There are various surgical techniques including the use of blue dye, radioisotope or a combination of the two and whether pathological ultrastaging of dissected nodes is completed. Cormier and colleagues proposed an algorithm for SLNB, which was included in the NCCN guideline.[34] It suggests that all mapped sentinel nodes be excised and ultrastaged, all suspect nodes be removed regardless of mapping, if only unilateral mapping performed then contralateral lymph node dissection be performed, all procedures include parametrectomy en bloc with primary tumor resection. The authors evaluated this algorithm in 122 patients and were able to identify 100% of positive lymph nodes. However, the value of identifying micrometastases by ultrastaging is not clear.

Adjuvant Therapy

Following radical hysterectomy, the type of adjuvant therapy will depend on the patient's risk factors. Factors to consider include histology, tumour size, depth of stromal invasion, lymphovascular space invasion (LVSI), nodal status, parametrial margin, and vaginal margin. Patients with a negative nodal status, negative parametrial margins, and negative vaginal margins are considered low risk; for these patients, observation following surgery is an acceptable option.[13,18]

Patients are considered intermediate risk for relapse if they exhibit any of the following: squamous cell carcinoma, adenocarcinomas or adenosquamous carcinomas with any two of the following risk factors; any tumour size with over 2/3rd invasion and positive LVSI; or any tumour size > 4 cm with over 2/3rd invasion and negative LVSI. Whole pelvic radiotherapy with or without weekly cisplatin (6 cycles) should be considered for intermediate risk patients. For patients with adenocarcinoma or adenosquamous tumour plus one risk factor, there is uncertainty on the benefits of chemoradiation. A discussion with the radiation oncologist regarding the benefit of chemoradiotherapy may be required.[10,18] Follow up of a phase III randomized (Gynecologic Oncology Group) trial showed that among patients with stage IB cervical cancer with negative lymph nodes but with two or more of the following: > 1/3rd (deep) stromal invasion, capillary lymphatic space involvement, or ≥ 4 cm tumour diameter, postoperative external-beam irradiation to the standard pelvic field improved survival versus radical hysterectomy and pelvic lymphadenectomy alone (observation). There were 27 deaths among the radiotherapy group versus 40 deaths in the observation group (overall survival HR was 0.70, 90% CI 0.45-1.05, p = 0.074).[10,35] A Cochrane Collaboration meta-analysis in 2009 found no significant difference in survival among patients who received adjuvant radiation or no further treatment, at five years (RR 0.8; 95% CI 0.3-2.4); however, patients who received radiation

had a significantly lower rate of progression (RR 0.6; 95% CI 0.4-0.5), as compared to those with no further treatment.[21]

Patients are considered high risk for relapse if they exhibit positive pelvic nodes and/or positive margins. These patients should be treated with whole pelvic radiotherapy with or without brachytherapy plus weekly cisplatin for six cycles.[13,18]

Neoadjuvant chemotherapy has been proposed for locally advanced cervical cancer. Several reviews have examined the use of neoadjuvant chemotherapy for cervical cancer, however, they have not compared this treatment to current standard practice of chemoradiation.[36,37,38] In particular, a 2013 meta-analysis comparing neoadjuvant chemotherapy and surgery vs. primary surgery, in five trails, found reduced rates of large tumour size, lymph node metastasis, need of adjuvant radiation therapy, distant metastases, but no difference in recurrence, progression free survival and overall survival .[38] There is a lack of conclusive evidence for the benefit of neoadjuvant chemotherapy. A multi-centre phase III trial (EORTC55994) is currently investigating the use of neoadjuvant chemotherapy prior to surgery compared to current practice of cisplatin-based chemoradiation. The results of this trial should provide evidence to clarify the effectiveness of neoadjuvant chemotherapy.

Management of Recurrent Disease

Treatment of cervical cancer recurrence is directed by whether disease is confined to the pelvis or disseminated to extra-pelvic organs. Patients with curable pelvic recurrences are treated with radical radiotherapy, with or without cisplatin, if previously treated with surgery. If previously treated with radical radiotherapy then pelvic exenteration is considered.[39] Patients with incurable or extra-pelvic recurrences are offered enrolment in a clinical trial or treated with palliative chemotherapy and/or radiotherapy.

Recommended chemotherapy includes single agent carboplatin or cisplatin. Combination chemotherapy can also be offered. The Gynecologic Oncology Group and others[11,39,40] have recommended the combination of cisplatin with topotecan; however, progression free survival is only 4.6 months compared to 2.9 months for single agent cisplatin and overall survival is 9.4 months compared to 6.5 months for cisplatin alone. There is also significant toxicity with this combination.[41,42] In a phase III clinical trial among patients with advanced or recurrent stage IVB cervical cancer (n = 513), the combination of paclitaxel and cisplatin outperformed the combinations of vinorelbine and cisplatin, gemcitabine and cisplatin, and topotecan and cisplatin in terms of overall response rate (29.1% vs. 25.9% vs. 22.3% vs. 23.4%, respectively) and was not inferior in terms of risk of progression or risk of death.[43,44] Similar response rates have been reported elsewhere.[45] Phase II clinical trial data suggests that the addition of ifosamide to cisplatin and paclitaxel may be more effective for recurrent or metastatic disease; among 153 patients treated with either this triplet combination or with ifosamide and cisplatin, the overall response rates were 59% and 33%, respectively ($p < 0.01$). Furthermore, progression free and overall survival times were significantly longer among patients who received the triplet regimen (7.9 vs. 6.3 months and 15.4 vs. 13.2 months, respectively).[46]

Follow Up and Surveillance

There are no randomized controlled trials to inform best practice for the follow up of patients with cervical cancer; rather, recommendations are based on data from retrospective studies. Given that the majority (62 to 89%) of cervical cancer recurrences are detected within two years and nearly all (89 to 99%) are

detected within five years,[47] the most rigorous follow up should be done during the first five years following treatment.[12] A systematic review of 13 trials showed that vaginal vault cytology detected asymptomatic recurrent disease in only 0 to 17% of patients, whereas asymptomatic recurrent disease was detected using physical exam in 29 to 71% of patients.[47] Therefore, vaginal vault cytology may be warranted once yearly only.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
CI	confidence interval
EBRT	external beam radiotherapy
Gy	Gray; unit of radiation
HR	hazard ratio
HDR	high dose rate
IMRT	intensity modulated radiotherapy
LVSI	lymphovascular space involvement
PA	para-aortic
PDR	pulsed dose rate
PALND	para-aortic lymphadenectomy
PLND	pelvic lymphadenectomy
RT	radiotherapy
RR	relative risk
SLNB	sentinel lymph node biopsy

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerCare Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2017. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Gynecologic Oncology Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Gynecologic Oncology Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

REFERENCES

1. Canadian Cancer Society. Canadian Cancer Statistics, 2009. Available at: www.cancer.ca/Canada-wide/About%20cancer/Cancer%20statistics/~/media/CCS/Canada%20wide/Files%20List/English%20files%20heading/pdf%20not%20in%20publications%20section/Stats%202009E%20Cdn%20Cancer.ashx. Accessed 05/10, 2010.
2. Surveillance & Reporting. 2012 Report on Cancer Statistics in Alberta. Edmonton: CancerControl AB, Alberta Health Services; 2015.
3. American Cancer Society. Detailed Guide: Ovarian Cancer. Available at: http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_are_the_key_statistics_for_ovarian_cancer_33.asp?rnav=cri. Accessed 05/10, 2010.
4. Pisani P, Bray F, Parkin DM. Estimates of the world-wide prevalence of cancer for 25 sites in the adult population. Int J Cancer 2002 Jan 1;97(1):72-81 PubMed ID 11774246.
5. Shepherd JH. Revised FIGO staging for gynaecological cancer. Br J Obstet Gynaecol 1989 Aug;96(8):889-892 PubMed ID 2775686.
6. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 2009 May;105(2):103-104 PubMed ID 19367689.
7. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer. ;Version 2.2015.
8. Haie-Meder C, Morice P, Castiglione M on behalf of the ESMO Guidelines Working Group. Cervical cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. Annals of Oncology 20 (Suppl 4): iv27–iv28, 2009. Available at: http://annonc.oxfordjournals.org/content/20/suppl_4/iv27.full. Accessed 07/24, 2014.
9. BC Cancer Agency. Cancer Management Guidelines: Gynecology: Uterine Cervix: Management. Available at: www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Gynecology/UterineCervix1of2/default.htm. Accessed 05/3, 2010.
10. Lukka H, Hirte H, Fyles A and members of the Gynecology Cancer Disease Site Group. Primary Treatment for Locally Advanced Cervical Cancer: Concurrent Platinum-based Chemotherapy and Radiation. Report #4-5, June 2004. Available at: https://www.cancercare.on.ca/common/pages/UserFile.aspx?serverId=6&path=/File%20Database/CCO%20Files/PEBC/pebc4-5f.pdf. Accessed 07/24, 2014.
11. Hirte H, Strychowsky J, Oliver T and the Gynecology Cancer Disease Site Group. Chemotherapy for recurrent, Metastatic, or Persistent Cervical Cancer: A Clinical Practice Guideline: A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO). Evidence-Based Series #4-20. Available at: https://www.cancercare.on.ca/common/pages/UserFile.aspx?serverId=6&path=/File%20Database/CCO%20Files/PEBC/pebc4-20f.pdf. Accessed 07/24, 2014.
12. Elit L, Kennedy EB, Fyles A, Metser U. Follow-up for Cervical Cancer. 2015 May 12;Program in Evidence-Based Care Guideline 4-16 Version 2.
13. Tom Baker Cancer Centre: Management of Gynecological Malignancies. 2008.
14. Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2013 Jul 1;31(19):2500-2510 PubMed ID 23715580.
15. Walji N, Chue AL, Yap C, Rogers LJ, El-Modir A, Chan KK, et al. Is there a role for adjuvant hysterectomy after suboptimal concurrent chemoradiation in cervical carcinoma? Clin Oncol (R Coll Radiol) 2010 Mar;22(2):140-146 PubMed ID 20045300.
16. Lertsanguansinchai P, Lertbutsayanukul C, Shotelersuk K, Khorprasert C, Rojpornpradit P, Chottetanaprasith T, et al. Phase III randomized trial comparing LDR and HDR brachytherapy in treatment of cervical carcinoma. Int J Radiat Oncol Biol Phys 2004 Aug 1;59(5):1424-1431 PubMed ID 15275728.
17. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol 2008 Dec 10;26(35):5802-5812 PubMed ID 19001332.
18. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Cervical Cancer, v.1.2010. Available at: http://www.nccn.org/professionals. Accessed 05/13, 2010.

19. Rogers LJ, Luesley DM. Stage IA2 cervical carcinoma: how much treatment is enough? Int J Gynecol Cancer 2009 Dec;19(9):1620-1624 PubMed ID 19994472.
20. Vizkeleti J, Pete I, Vereczkey I, Frohlich G, Horvath K, Varga S, et al. Complete pathologic remission after preoperative high-dose brachytherapy in patients with operable cervical cancer: preliminary results of a prospective randomized study. Magy Onkol 2012 Sep;56(3):171-177 PubMed ID 23008825.
21. Pearcey R, Brundage M, Drouin P, Jeffrey J, Johnston D, Lukka H, et al. Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. J Clin Oncol 2002 Feb 15;20(4):966-972 PubMed ID 11844818.
22. Kantardzic N, Beslija S, Begic D. Comparative parameters of myelotoxicity in patients treated with simultaneous chemotherapy and radiotherapy or only radiotherapy. Med Arh 2004;58(1):19-22 PubMed ID 15017898.
23. Cikaric S, Petrovic-Stupar S, Marjanov I. Radiotherapy vs. radiotherapy + chemotherapy of advanced cervical cancer: Regression of tumour, early and late sequalaes, relapses of disease and 3 years survival (the third phase). Available at: http://www.onk.ns.ac.rs/archive/vol13/PDFVol13/V13s1p34.pdf. Accessed 07/24, 2014.
24. Keys HM, Bundy BN, Stehman FB, Okagaki T, Gallup DG, Burnett AF, et al. Radiation therapy with and without extrafascial hysterectomy for bulky stage IB cervical carcinoma: a randomized trial of the Gynecologic Oncology Group. Gynecol Oncol 2003 Jun;89(3):343-353 PubMed ID 12798694.
25. Lanciano R, Calkins A, Bundy BN, Parham G, Lucci JA,3rd, Moore DH, et al. Randomized comparison of weekly cisplatin or protracted venous infusion of fluorouracil in combination with pelvic radiation in advanced cervix cancer: a gynecologic oncology group study. J Clin Oncol 2005 Nov 20;23(33):8289-8295 PubMed ID 16230678.
26. Rose PG, Ali S, Watkins E, Thigpen JT, Deppe G, Clarke-Pearson DL, et al. Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2007 Jul 1;25(19):2804-2810 PubMed ID 17502627.
27. Brockbank E, Kokka F, Bryant A, Pomel C, Reynolds K. Pre-treatment surgical para-aortic lymph node assessment in locally advanced cervical cancer. Cochrane Database Syst Rev 2013 Mar 28;3:CD008217 PubMed ID 23543561.
28. Biewenga P, van der Velden J, Mol BW, Stalpers LJ, Schilthuis MS, van der Steeg JW, et al. Prognostic model for survival in patients with early stage cervical cancer. Cancer 2011 Feb 15;117(4):768-776 PubMed ID 20922801.
29. Creasman WT, Kohler MF. Is lymph vascular space involvement an independent prognostic factor in early cervical cancer? Gynecol Oncol 2004 Feb;92(2):525-529 PubMed ID 14766243.
30. Matsuura Y, Kawagoe T, Toki N, Tanaka M, Kashimura M. Long-standing complications after treatment for cancer of the uterine cervix--clinical significance of medical examination at 5 years after treatment. Int J Gynecol Cancer 2006 Jan-Feb;16(1):294-297 PubMed ID 16445648.
31. Wu Y, Li Z, Wu H, Yu J. Sentinel lymph node biopsy in cervical cancer: A meta-analysis. Mol Clin Oncol 2013 Nov;1(6):1025-1030 PubMed ID 24649288.
32. Kadkhodayan S, Hasanzadeh M, Treglia G, Azad A, Yousefi Z, Zarifmahmoudi L, et al. Sentinel node biopsy for lymph nodal staging of uterine cervix cancer: a systematic review and meta-analysis of the pertinent literature. Eur J Surg Oncol 2015 Jan;41(1):1-20 PubMed ID 25454828.
33. Bats AS, Mathevet P, Buenerd A, Orliaguet I, Mery E, Zerdoud S, et al. The sentinel node technique detects unexpected drainage pathways and allows nodal ultrastaging in early cervical cancer: insights from the multicenter prospective SENTICOL study. Ann Surg Oncol 2013 Feb;20(2):413-422 PubMed ID 22911367.
34. Cormier B, Diaz JP, Shih K, Sampson RM, Sonoda Y, Park KJ, et al. Establishing a sentinel lymph node mapping algorithm for the treatment of early cervical cancer. Gynecol Oncol 2011 Aug;122(2):275-280 PubMed ID 21570713.
35. Rotman M, Sedlis A, Piedmonte MR, Bundy B, Lentz SS, Muderspach LI, et al. A phase III randomized trial of postoperative pelvic irradiation in Stage IB cervical carcinoma with poor prognostic features: follow-up of a gynecologic oncology group study. Int J Radiat Oncol Biol Phys 2006 May 1;65(1):169-176 PubMed ID 16427212.
36. Tierney J, Rydzewska L. Neoadjuvant chemotherapy for locally advanced cervix cancer. Cochrane Database of Systematic Reviews 2015;2.
37. Rydzewska L, Tierney J, Vale CL, Symonds PR. Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer. Cochrane Database Syst Rev 2012 Dec 12;12:CD007406 PubMed ID 23235641.

38. Kim HS, Sardi JE, Katsumata N, Ryu HS, Nam JH, Chung HH, et al. Efficacy of neoadjuvant chemotherapy in patients with FIGO stage IB1 to IIA cervical cancer: an international collaborative meta-analysis. Eur J Surg Oncol 2013 Feb;39(2):115-124 PubMed ID 23084091.
39. National Comprehensive Cancer Network. Guidelines and Clinical Resources: Cervical Cancer. V1.2012. Available at: http://www.nccn.org.
40. National Institute for Health and Clinical Excellence (NICE). Topotecan for the treatment of recurrent and stage IVB cervical cancer. London (UK): National Institute for Health and Clinical Excellence (NICE); 2009 Oct. 35 p. (Technology appraisal guidance; no. 183). Available at: http://www.guideline.gov/content.aspx?id=15544. Accessed 07/24, 2014.
41. Long HJ,3rd, Bundy BN, Grendys EC,Jr, Benda JA, McMeekin DS, Sorosky J, et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. J Clin Oncol 2005 Jul 20;23(21):4626-4633 PubMed ID 15911865.
42. Monk BJ, Huang HQ, Cella D, Long HJ,3rd, Gynecologic Oncology Group Study. Quality of life outcomes from a randomized phase III trial of cisplatin with or without topotecan in advanced carcinoma of the cervix: a Gynecologic Oncology Group Study. J Clin Oncol 2005 Jul 20;23(21):4617-4625 PubMed ID 15911864.
43. Cella D, Huang HQ, Monk BJ, Wenzel L, Benda J, McMeekin DS, et al. Health-related quality of life outcomes associated with four cisplatin-based doublet chemotherapy regimens for stage IVB recurrent or persistent cervical cancer: a Gynecologic Oncology Group study. Gynecol Oncol 2010 Dec;119(3):531-537 PubMed ID 20837359.
44. Monk BJ, Sill MW, McMeekin DS, Cohn DE, Ramondetta LM, Boardman CH, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 2009 Oct 1;27(28):4649-4655 PubMed ID 19720909.
45. Moore DH, Blessing JA, McQuellon RP, Thaler HT, Cella D, Benda J, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol 2004 Aug 1;22(15):3113-3119 PubMed ID 15284262.
46. Mountzios G, Dimopoulos MA, Bamias A, Vourli G, Kalofonos H, Aravantinos G, et al. Randomized multicenter phase II trial of cisplatin and ifosfamide with or without paclitaxel in recurrent or metastatic carcinoma of the uterine cervix: a Hellenic Cooperative Oncology Group (HeCOG) study. Ann Oncol 2009 Aug;20(8):1362-1368 PubMed ID 19457937.
47. 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 Sep;114(3):528-535 PubMed ID 19560188.

ADDITIONAL REFERENCES IDENTIFIED BY THE LITERATURE SEARCH

Alberts DS, Blessing JA, Landrum LM, Warshal DP, Martin LP, Rose SL, Bonebrake AJ, Ramondetta LM. Phase II trial of nab-paclitaxel in the treatment of recurrent or persistent advanced cervix cancer: A gynecologic oncology group study. Gynecol Oncol. 2012 Dec;127(3):451-5. Epub 2012 Sep 14.

Armstrong DK, Blessing JA, Rader J, Sorosky JI; Gynecologic Oncology Group Study. A randomized phase II evaluation of bryostatin-1 (NSC #339555) in persistent or recurrent squamous cell carcinoma of the cervix: A Gynecologic Oncology Group Study. Invest New Drugs. 2003 Nov;21(4):453-7.

Benedetti-Panici P, Greggi S, Colombo A, et al. Neoadjuvant chemotherapy and radical surgery versus exclusive radiotherapy in locally advanced squamous cell cervical cancer: results from the Italian multicenter randomized study. J Clin Oncol. 2002 Jan 1;20(1):179-88.

Bloss JD, Blessing JA, Behrens BC, et al. Randomized trial of cisplatin and ifosfamide with or without bleomycin in squamous carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol. 2002 Apr 1;20(7):1832-7.

Brave M, Dagher R, Farrell A, et al. Topotecan in combination with cisplatin for the treatment of stage IVB, recurrent, or persistent cervical cancer. Oncology (Williston Park). 2006;20(11):1401-4, 1410-11.

Buda A, Fossati R, Colombo N, et al. Randomized trial of neoadjuvant chemotherapy comparing paclitaxel, ifosfamide, and cisplatin with ifosfamide and cisplatin followed by radical surgery in patients with locally advanced squamous cell cervical carcinoma: the SNAP01 (Studio Neo-Adjuvante Portio) Italian Collaborative Study. J Clin Oncol. 2005 Jun 20;23(18):4137-45.

Cadron I, Jakobsen A, Vergote I. Report of an early stopped randomized trial comparing cisplatin vs. cisplatin/ ifosfamide/ 5-fluorouracil in recurrent cervical cancer. Gynecol Obstet Invest. 2005;59(3):126-9.

Cai HB, Chen HZ, Yin HH. Randomized study of preoperative chemotherapy versus primary surgery for stage IB cervical cancer. J Obstet Gynaecol Res. 2006 Jun;32(3):315-23.

Chang TC, Lai CH, Hong JH, et al. Randomized trial of neoadjuvant cisplatin, vincristine, bleomycin, and radical hysterectomy versus radiation therapy for bulky stage IB and IIA cervical cancer. J Clin Oncol. 2000 Apr;18(8):1740-7.

Chatani M, Matayoshi Y, Masaki N, et al. A prospective randomized study concerning the point A dose in high-dose rate intracavitary therapy for carcinoma of the uterine cervix. The final results. Strahlenther Onkol. 1994 Nov;170(11):636-42.

Chen H, Liang C, Zhang L, et al. Clinical efficacy of modified preoperative neoadjuvant chemotherapy in the treatment of locally advanced (stage IB2 to IIB) cervical cancer: randomized study. Gynecol Oncol. 2008 Sep;110(3):308-15.

Chumworathayi B, Suprasert P, Charoenkwan K, et al. Weekly versus three-weekly cisplatin as an adjunct to radiation therapy in high-risk stage I-IIA cervical cancer after surgery: a randomized comparison of treatment compliance. J Med Assoc Thai. 2005 Nov;88(11):1483-92.

Curtin JP, Hoskins WJ, Venkatraman ES, et al. Adjuvant chemotherapy versus chemotherapy plus pelvic irradiation for high-risk cervical cancer patients after radical hysterectomy and pelvic lymphadenectomy (RH-PLND): a randomized phase III trial. Gynecol Oncol. 1996 Apr;61(1):3-10.

Dayes IS, Abuzallouf S. Local tumour control in women with carcinoma of the cervix treated with the addition of nitroimidazole agents to radiotherapy: a meta-analysis. Br J Radiol. 2005 Sep;78(933):777-82.

Dobrowsky W, Huigol NG, Jayatilake RS, et al. AK-2123 (Sanazol) as a radiation sensitizer in the treatment of stage III cancer cervix: initial results of an IAEA multicentre randomized trial. J Cancer Res Ther. 2005 Apr-Jun;1(2):75-8.

Dueñas-González A, Cetina-Perez L, Lopez-Graniel C, et al. Pathologic response and toxicity assessment of chemoradiotherapy with cisplatin versus cisplatin plus gemcitabine in cervical cancer: a randomized Phase II study. Int J Radiat Oncol Biol Phys. 2005 Mar 1;61(3):817-23.

Eddy GL, Bundy BN, Creasman WT, et al. Treatment of ("bulky") stage IB cervical cancer with or without neoadjuvant vincristine and cisplatin prior to radical hysterectomy and pelvic/para-aortic lymphadenectomy: a phase III trial of the gynecologic oncology group. Gynecol Oncol. 2007;106(2):362-9.

Eifel PJ, Winter K, Morris M, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. J Clin Oncol. 2004 Mar 1;22(5):872-80.

el-Baradie M, Inoue T, Inoue T, et al. HDR and MDR intracavitary treatment for carcinoma of the uterine cervix. A prospective randomized study. Strahlenther Onkol. 1997 Mar;173(3):155-62.

Franckena M, Stalpers LJ, Koper PC, et al. Long-term improvement in treatment outcome after radiotherapy and hyperthermia in locoregionally advanced cervix cancer: an update of the Dutch Deep Hyperthermia Trial. Int J Radiat Oncol Biol Phys. 2008 Mar 15;70(4):1176-82. Epub 2007 Sep 19.

Garcia AA, Blessing JA, Darcy KM, et al. Phase II clinical trial of capecitabine in the treatment of advanced, persistent or recurrent squamous cell carcinoma of the cervix with translational research: A gynecologic oncology group study. 2007. Gynecologic Oncology. 104(3): 572-579.

Hareyama M, Sakata K, Oouchi A, et al. High-dose-rate versus low-dose-rate intracavitary therapy for carcinoma of the uterine cervix: a randomized trial. Cancer. 2002 Jan 1;94(1):117-24.

Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med. 1999 Apr 15;340(15):1154-61.

Kim YS, Shin SS, Nam JH, et al. Prospective randomized comparison of monthly fluorouracil and cisplatin versus weekly cisplatin concurrent with pelvic radiotherapy and high-dose rate brachytherapy for locally advanced cervical cancer. Gynecol Oncol. 2008 Jan;108(1):195-200.

Lai CH, Tang SG, Chang TC, et al. Implications of a failed prospective trial of adjuvant therapy after radical hysterectomy for stage Ib-IIa cervical carcinoma with pelvic node metastases. Changgeng Yi Xue Za Zhi. 1998 Sep;21(3):291-9.

Lai CH, Huang KG, Hong JH, et al. Randomized trial of surgical staging (extraperitoneal or laparoscopic) versus clinical staging in locally advanced cervical cancer. Gynecol Oncol. 2003 Apr;89(1):160-7.

Lahousen M, Haas J, Pickel H, et al. Chemotherapy versus radiotherapy versus observation for high-risk cervical carcinoma after radical hysterectomy: A randomized, prospective, multicenter trial. Gynecol Oncol. 1999 May;73(2):196-201.

Lambin P, Gerbaulet A, Kramar A, et al. Phase III trial comparing two low dose rates in brachytherapy of cervix carcinoma: report at two years. Int J Radiat Oncol Biol Phys. 1993 Feb 15;25(3):405-12.

Landoni F, Maneo A, Colombo A, et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet. 1997 Aug 23;350(9077):535-40.

Landoni F, Maneo A, Cormio G, et al. Class II versus class III radical hysterectomy in stage IB-IIA cervical cancer: a prospective randomized study. Gynecol Oncol. 2001 Jan;80(1):3-12.

Lertsanguansinchai P, Lertbutsayanukul C, Shotelersuk K, et al. Phase III randomized trial comparing LDR and HDR brachytherapy in treatment of cervical carcinoma. Int J Radiat Oncol Biol Phys. 2004 Aug 1;59(5):1424-31.

Lira-Puerto V, Silva A, Morris M, Martinez R, Groshen S, Morales-Canfield F, Tenorio F, Muggia F. Phase II trial of carboplatin or iproplatin in cervical cancer. Cancer Chemother Pharmacol. 1991;28(5):391-6.

Lissoni AA, Colombo N, Pellegrino A, et al. A phase II, randomized trial of neo-adjuvant chemotherapy comparing a three-drug combination of paclitaxel, ifosfamide, and cisplatin (TIP) versus paclitaxel and cisplatin (TP) followed by radical surgery in patients with locally advanced squamous cell cervical carcinoma: the Snap-02 Italian Collaborative Study. Ann Oncol. 2009 Apr;20(4):660-5. Epub 2009 Jan 30.

Long HJ 3rd, Rayson S, Podratz KC, et al. Long-term survival of patients with advanced/recurrent carcinoma of cervix and vagina after neoadjuvant treatment with methotrexate, vinblastine, doxorubicin, and cisplatin with or without the addition of molgramostim, and review of the literature. Am J Clin Oncol. 2002 Dec;25(6):547-51.

Long HJ 3rd, Monk BJ, Huang HQ, et al; Gynecologic Oncology Group. Clinical results and quality of life analysis for the MVAC combination (methotrexate, vinblastine, doxorubicin, and cisplatin) in carcinoma of the uterine cervix: A Gynecologic Oncology Group study. Gynecol Oncol. 2006 Mar;100(3):537-43.

Lorvidhaya V, Chitapanarux I, Sangruchi S, et al. Concurrent mitomycin C, 5-fluorouracil, and radiotherapy in the treatment of locally advanced carcinoma of the cervix: a randomized trial. Int J Radiat Oncol Biol Phys. 2003 Apr 1;55(5):1226-32.

Miller DS, Blessing JA, Bodurka DC, et al. Evaluation of pemetrexed (Alimta, LY231514) as second line chemotherapy in persistent or recurrent carcinoma of the cervix: A Phase II study of the Gynecologic Oncology Group. Gynecologic Oncology. 110 (1) (pp 65-70), 2008.

Mitra D, Ghosh B, Kar A, et al. Role of chemoradiotherapy in advanced carcinoma cervix. J Indian Med Assoc. 2006 Aug;104(8):432, 434, 436 passim.

Modarress M, Maghami FQ, Golnavaz M, et al. Comparative study of chemoradiation and neoadjuvant chemotherapy effects before radical hysterectomy in stage IB-IIB bulky cervical cancer and with tumor diameter greater than 4 cm. Int J Gynecol Cancer. 2005;15(3):483-8.

Monk BJ, Mas Lopez L, Zarba JJ, et al. Phase II, open-label study of pazopanib or lapatinib monotherapy compared with pazopanib plus lapatinib combination therapy in patients with advanced and recurrent cervical cancer. J Clin Oncol. 2010 Aug 1;28(22):3562-9. Epub 2010 Jul 6.

Moore DH, Blessing JA, McQuellon RP, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol. 2004 Aug 1;22(15):3113-9.

Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med. 1999 Apr 15;340(15):1137-43.

Nagy V, Coza O, Ordeanu C, et al. Radiotherapy versus concurrent 5-day cisplatin and radiotherapy in locally advanced cervical carcinoma. Long-term results of a phase III randomized trial. Strahlenther Onkol. 2009 Mar;185(3):177-83. Epub 2009 Mar 28.

Nam TK, Ahn SJ. A prospective randomized study on two dose fractionation regimens of high-dose-rate brachytherapy for carcinoma of the uterine cervix: comparison of efficacies and toxicities between two regimens. J Korean Med Sci. 2004 Feb;19(1):87-94.

Napolitano U, Imperato F, Mossa B, et al. The role of neoadjuvant chemotherapy for squamous cell cervical cancer (Ib-IIIb): a long-term randomized trial. Eur J Gynaecol Oncol. 2003;24(1):51-9.

Noda K, Ohashi Y, Sugimori H, et al. Phase III double-blind randomized trial of radiation therapy for stage IIIb cervical cancer in combination with low- or high-dose Z-100: treatment with immunomodulator, more is not better. Gynecol Oncol. 2006 Jun;101(3):455-63. Epub 2005 Dec 19.

Obermair A, Gebski V, Frumovitz M, et al. A phase III randomized clinical trial comparing laparoscopic or robotic radical hysterectomy with abdominal radical hysterectomy in patients with early stage cervical cancer. J Minim Invasive Gynecol. 2008 Sep-Oct;15(5):584-8.

Piver M.S., Ghamande S.A., Eltabbakh G.H., O'Neill-Coppola C. First-line chemotherapy with paclitaxel and platinum for advanced and recurrent cancer of the cervix - A phase II study. Gynecol Onc. 75(3):334-337.

Rosa DD, Medeiros LR, Edelweiss MI, et al. Adjuvant platinum-based chemotherapy for early stage cervical cancer. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD005342.

Rotman M, Pajak TF, Choi K, et al. Prophylactic extended-field irradiation of para-aortic lymph nodes in stages IIB and bulky IB and IIA cervical carcinomas. Ten-year treatment results of RTOG 79-20. JAMA. 1995 Aug 2;274(5):387-93.

Saito I, Kitagawa R, Fukuda H, et al. A phase III trial of paclitaxel plus carboplatin versus paclitaxel plus cisplatin in stage IVB, persistent or recurrent cervical cancer: Gynecologic Cancer Study Group/Japan Clinical Oncology Group Study (JCOG0505). Jpn J Clin Oncol. 2010 Jan;40(1):90-3. Epub 2009 Oct 12.

Sardi JE, Giaroli A, Sananes C, et al. Long-term follow-up of the first randomized trial using neoadjuvant chemotherapy in stage Ib squamous carcinoma of the cervix: the final results. Gynecol Oncol. 1997 Oct;67(1):61-9.

Sedlis A, Bundy BN, Rotman MZ, et al. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. Gynecol Oncol. 1999 May;73(2):177-83.

Stehman FB, Ali S, Keys HM, et al. Radiation therapy with or without weekly cisplatin for bulky stage 1B cervical carcinoma: follow-up of a Gynecologic Oncology Group trial. Am J Obstet Gynecol. 2007 Nov;197(5):503.e1-6.

Symonds RP, Habeshaw T, Reed NS, et al. The Scottish and Manchester randomised trial of neo-adjuvant chemotherapy for advanced cervical cancer. Eur J Cancer. 2000 May;36(8):994-1001.

Tacev T, Ptácková B, Strnad V. Californium-252 (252Cf) versus conventional gamma radiation in the brachytherapy of advanced cervical carcinoma long-term treatment results of a randomized study. Strahlenther Onkol. 2003 Jun; 179(6):377-84.

Torres MA, Jhingran A, Thames HD Jr, et al. Comparison of treatment tolerance and outcomes in patients with cervical cancer treated with concurrent chemoradiotherapy in a prospective randomized trial or with standard treatment. Int J Radiat Oncol Biol Phys. 2008 Jan 1;70(1):118-25. Epub 2007 Sep 14.

van Luijk IF, Coens C, van der Burg MEL, et al. Phase II study of bleomycin, vindesine, mitomycin C and cisplatin (BEMP) in recurrent or disseminated squamous cell carcinoma of the uterine cervix. 2007. Annals of Oncology. 18(2):275-281.

Veerasarn V, Lorvidhaya V, Kamnerdsupaphon P, et al. A randomized phase III trial of concurrent chemoradiotherapy in locally advanced cervical cancer: preliminary results. Gynecol Oncol. 2007 Jan;104(1):15-23. Epub 2006 Sep 25.

Weiss GR, Green S, Hannigan EV, et al. A phase II trial of carboplatin for recurrent or metastatic squamous carcinoma of the uterine cervix: a Southwest Oncology Group study. Gynecol Oncol. 1990 Dec;39(3):332-6.

Weiss GR, Green S, Hannigan EV, et al. A phase II trial of cisplatin and 5-fluorouracil with allopurinol for recurrent or metastatic carcinoma of the uterine cervix: a Southwest Oncology Group trial. Gynecol Oncol. 1990 Jun;37(3):354-8.

Weiss GR, Liu PY, Alberts DS, et al. 13-cis-retinoic acid or all-trans-retinoic acid plus interferon-alpha in recurrent cervical cancer: a Southwest Oncology Group phase II randomized trial. Gynecol Oncol. 1998 Dec;71(3):386-90.

Weiss GR, Liu PY, O'Sullivan J, et al. A randomized phase II trial of trimetrexate or didemnin B for the treatment of metastatic or recurrent squamous carcinoma of the uterine cervix: a Southwest Oncology Group trial. Gynecol Oncol. 1992 Jun;45(3):303-6.

Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol. 1999 May;17(5):1339-48.

APPENDIX

Staging of cancer of the uterine cervix is based on the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) 2010:

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 of ≤3.0 mm in depth and extension of ≤7.0 mm
  - IA2 Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm
- IB Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA*
  - IB1 Clinically visible lesion ≤4.0 cm in greatest dimension
  - IB2 Clinically visible lesion >4.0 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 ≤4.0 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

* 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 not >7.00 mm. Depth of invasion should not be >5.00mmtaken 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.