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# Cancer of the Uterine Cervix

**Effective Date: January, 2021**

Cancer Care Alberta

Clinical Practice Guideline GYNE-004 – Version 6
www.ahs.ca/guru

## 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

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

## 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] Tom Baker Cancer Centre[13] and the American Society of Clinical Oncology (ASCO) [3]. 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, 2015 and again in 2020. 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. In 2020 the review focused on FIGO staging and recommendation for cervical examination and included total of 7 studies.

## 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*** *(Level of Evidence: I Strength of Recommendation: A )*[5-7,13,17]

Preferred options include:

- Invasive carcinoma <4 cm in greatest dimension
- 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:

- Invasive carcinoma ≥4 cm in greatest dimension
- 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:

- Invasive carcinoma ≥5.0 mm depth of invasion and <2.0 cm in greatest dimension
- 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:

- Invasive carcinoma ≥2.0 cm and <4.0 cm in greatest dimension
- 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

***FIGO Stage IB3:***

- Invasive carcinoma ≥4 cm in greatest dimension

- 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*

***FIGO Stage IIA1***

- Invasive carcinoma <4.0 cm in greatest dimension

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***

- Invasive carcinoma ≥4.0 cm in greatest dimension

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>

1. Consider the following risk factors when deciding on appropriate treatment options: *(Level of Evidence: III Strength of Recommendation: C )*[7,10,]

- 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

Radiation Therapy

Radiation therapy should be administered as follows: *(Level of Evidence: IV Strength of Recommendation: D )*[14]

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.*

Special Clinical Scenarios

1. 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 *(Level of Evidence: IV Strength of Recommendation: D )*[14]
2. 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) *(Level of Evidence: I Strength of Recommendation: A )*[15]

Adjuvant Chemotherapy

2. 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 EBR. *(Level of Evidence: II Strength of Recommendation: B )*[17,10,33]

***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; 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.

Vaginal or cervical vault cytology examination is recommended annually except in patients treated with radiotherapy; there is little evidence to support the routine use of vaginal or cervical vault cytology in patients treated with radiotherapy. Pap smears are not substitute for a careful pelvic examination *(Level of Evidence: II Strength of Recommendation: B )* [9,10,12].

## 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 [7,13]. 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 [17]. 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 [18].

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 [7, 8, 10,13]. A meta-analysis of 13 trials showed that chemoradiotherapy (versus radiotherapy alone) increased the disease free survival rate at five years by eight percent [16]. 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 [7]. 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 [14.] 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 [19-21], including three Gynecologic Oncology Group Trials [22-24] 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. Carboplatin is recommended if patient is intolerant to cisplatin containing chemoradiation [7].

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 [25].

There is a growing evidence that sentinel lymph node biopsy (SLNB) for nodal staging is useful for decreasing the need for pelvic lymphadenectomy in patients with early stage cervical cancer. Nodal stage is an important predictor of prognosis that can be used to guide treatment decisions [26,27]. Furthermore, SLNB may reduce the need for a lymphadenectomy, which is associated with complications such as lymphedema [28]. The feasibility of this procedure is demonstrated by a 2013 meta-analysis that included 17 studies with 1112 patients receiving SLNB [29]. 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% [30]. 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 [31]. 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. However based on the recent metaanalysis, Indocyanin green dye (ICG) showed similar overall and bilateral detection rate as dual blue dye/technetium-99 [32]. Another Phase III FILM trial also demostrated that ICG tracer identified more SLNs as compared to blue dye [33]. 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 [7,13.]

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; tumour size between 2 - 5 with over 1/3rd deep, middle or superficial invasion and positive LVSI; or any tumour size ≥ 4 cm with over 1/3rd middle or deep invasion and negative LVSI [7]. 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 [7,10.] 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: > 1/3$^{rd}$ (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) [10,33]. 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 [19].

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 [7,13.]

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 [36-38]. In particular, a 2013 meta-analysis comparing neoadjuvant chemotherapy and surgery vs. primary surgery, in five trials, 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) investigated the use of neoadjuvant chemotherapy prior to surgery compared to current practice of cisplatin-based chemoradiation. The results of this trial reveled no difference in 5-year OS between NACTS and CCRT, indicating that quality of life and long-term toxicity are important to decide optimal treatment. [39]

**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 [40]. 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 cisplatin as most effective agent. However carboplatin is recommended for the cisplatin intolerant patients [7]. First-line Combination chemotherapy can also be offered. The Gynecologic Oncology Group and others [7,11,37,38] have recommended the combination of cisplatin with paclitaxel and bevacizumab; or carboplatin with combination of paclitaxel and bevacizumab for the first-line combination therapy. A randomized phase III study showed a higher response rate and improved PFS with the combination of cisplatin/paclitaxel as compared to only cisplatin [41]. Another recent phase III trial showed the improvement in OS with combination of cisplatin/paclitaxel/bevacizumab [42].

Pembrolizumab has been approved by the FDA in the USA as second-line therapy for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] . However it has not as yet received approval in Canada [43]. 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 [44,45]. Similar response rates have been reported elsewhere [46]. 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) [47].

**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 [48], 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 [48]. Therefore, vaginal vault cytology may be warranted once yearly only.

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## Development and Revision History

This guideline was reviewed and endorsed by the Alberta GYNE Tumour Team. Members include [surgical oncologists, radiation oncologists, medical oncologists, dermatologists, nurses, pathologists, and pharmacists]. Evidence was selected and reviewed by a working group comprised of members from the Alberta Tumour Teams, external participants identified by the Working Group Lead, and a methodologist 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 2009 in 2011, 2012, 2013, 2015 and again in 2021

## Levels of Evidence

| | |
|---|---|
| **I** | Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity |
| **II** | Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity |
| **III** | Prospective cohort studies |
| **IV** | Retrospective cohort studies or case-control studies |
| **V** | Studies without control group, case reports, expert opinion |

## Strength of Recommendations

| | |
|---|---|
| **A** | Strong evidence for efficacy with a substantial clinical benefit; strongly recommended |
| **B** | Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended |
| **C** | Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional |
| **D** | Moderate evidence against efficacy or for adverse outcome; generally not recommended |
| **E** | Strong evidence against efficacy or for adverse outcome; never recommended |

## Maintenance

A formal review of the guideline will be conducted in 2022. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

## Abbreviations

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

## Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial GYNE Tumour 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.




## Funding Source

Financial support for the development of CancerCare Alberta's evidence-based clinical practice guidelines and supporting materials comes from the CancerCare Alberta operating budget; no outside commercial funding was received to support the development of this document.


All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the *Outpatient Cancer Drug Benefit Program Master List*.

## Conflict of Interest Statements

Dr. **Prafull Ghatage** has nothing to disclose.
Dr. **Gregg Nelson** has nothing to disclose.
Dr. **Helen Steed** has nothing to disclose.
**Ritu Sharma** has nothing to disclose.