PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

GYNECOLOGIC CANCER

CERVIX

Site Group: Gynecology – Cervix

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1. Introduction

Cancer of the cervix is the third most common gynecologic cancer diagnosis and cause of death among gynecologic cancers in North America. Cervical cancer is the tenth most common type of cancer in women (9.0 per 100,000 women) and ranked below the top ten causes of cancer mortality in North America (3.2 per 100,000). In contrast, cervical cancer is the most common gynecological malignancy in countries that do not have access to cervical cancer screening and prevention programs. As such, in several developing countries, cervical cancer is the second most common cancer (17.8 per 100,000 women) and the second most common cause of cancer deaths (9.8 per 100,000) among all types of cancer in women.

2. Prevention

Prevention of cervical carcinoma can be achieved by primary or secondary measures.

- **Primary prevention**: Vaccines have been developed that can protect women from HPV infections. So far, a vaccine that protects against HPV types 6, 11, 16 and 18 (Gardasil®) and one that protects against types 16 and 18 (Cervarix®) have been studied and approved for use. Both vaccines require a series of 3 injections over a 6-month period

- **Secondary prevention**: PAP smear screening may detect premalignant cells on cytology. This can be followed by a colposcopic examination where pathological diagnosis can be made. Pre-cancerous lesions may be treated using ablative or excisional procedures to prevent them from developing into invasive carcinoma.

3. Screening and Early Detection

Screening for cervical cancer can be achieved with a pap smear and/or an HPV test.

- **Pap smear**: The Papanicolaou test (pap test) is performed at time of a pelvic examination to collect cells from the cervix for cytological evaluation.

- **HPV testing**: An HPV test can be done along with a Pap test or as a separate test. Like a Pap test, the HPV test is done during a pelvic exam, using a small brush to collect a sample from the cervix. Women who are under age 30 are not usually tested for HPV because many women in this age group have transient HPV infections, which will resolve without treatment.

Regular screening is essential to the prevention and early detection of cervical cancer. The Ontario Cervical Cancer Screening Guidelines provide recommendations for screening schedule.
https://www.cancercare.on.ca/pcs/screening/cervscreening/

4. Diagnosis

FIGO Staging of Carcinoma of the Cervix Uteri 2009	
Stage 1	The carcinoma is strictly confined to the cervix (extension of the corpus would be disregarded
1A	Invasive carcinoma which can be diagnosed only by microscopy, with deepest incision <= 5mm and largest extension >= 7mm
1A1	Measured stromal invasion of <= 3.0mm in depth and extension of <= 7.0mm
1A2	Measured stromal invasion of >3.0mm and <5.0mm with an extension of <=7.0mm
1B	Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage 1A*
1B1	Clinically visible lesion ≤ 4.0cm in greatest dimension
1B2	Clinically visible lesion > 4.0cm in greatest dimension
Stage 2	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina
2A	Without parametrial invasion
2A1	Clinically visible lesion ≤ 4.0cm in greatest dimension
2A2	Clinically visible lesion > 4.0cm in greatest dimension
2B	With obvious parametrial invasion
Stage 3	The tumour extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney**
3A	Tumour involves lower third of the vagina, with no extension to the pelvic wall
3B	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney
Stage 4	The carcinoma has extended beyond the true pelvis or has involves (biopsy proven) the mucosa of the bladder or rectum
4A	Spread of growth to adjacent organs
4B	Spread to distant organs
*	All macroscopically visible lesions - even with superficial invasion - are allotted to stage 1B carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00mm and a horizontal extension of not >7.00mm. Depth of invasion should not be >5.00mm 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 those cases with "early (minimal) stromal invasion". The involvement of vascular/lymphatic spaces should not change the stage allotment.
**	On rectal examination, there is no cancer-free space between the tumour and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause.

Initial Evaluation

- Physical examination: Complete physical examination including weight and height (Body Mass Index), abdominal, pelvic and rectovaginal examination.
- Colposcopy may also be helpful to define the lesion.

- Biopsy
- Laboratory testing: CBC, electrolytes, creatinine, liver functions, as indicated
- Imaging: CT Thorax or CXR, CT abdomen/pelvis, Pelvic MRI

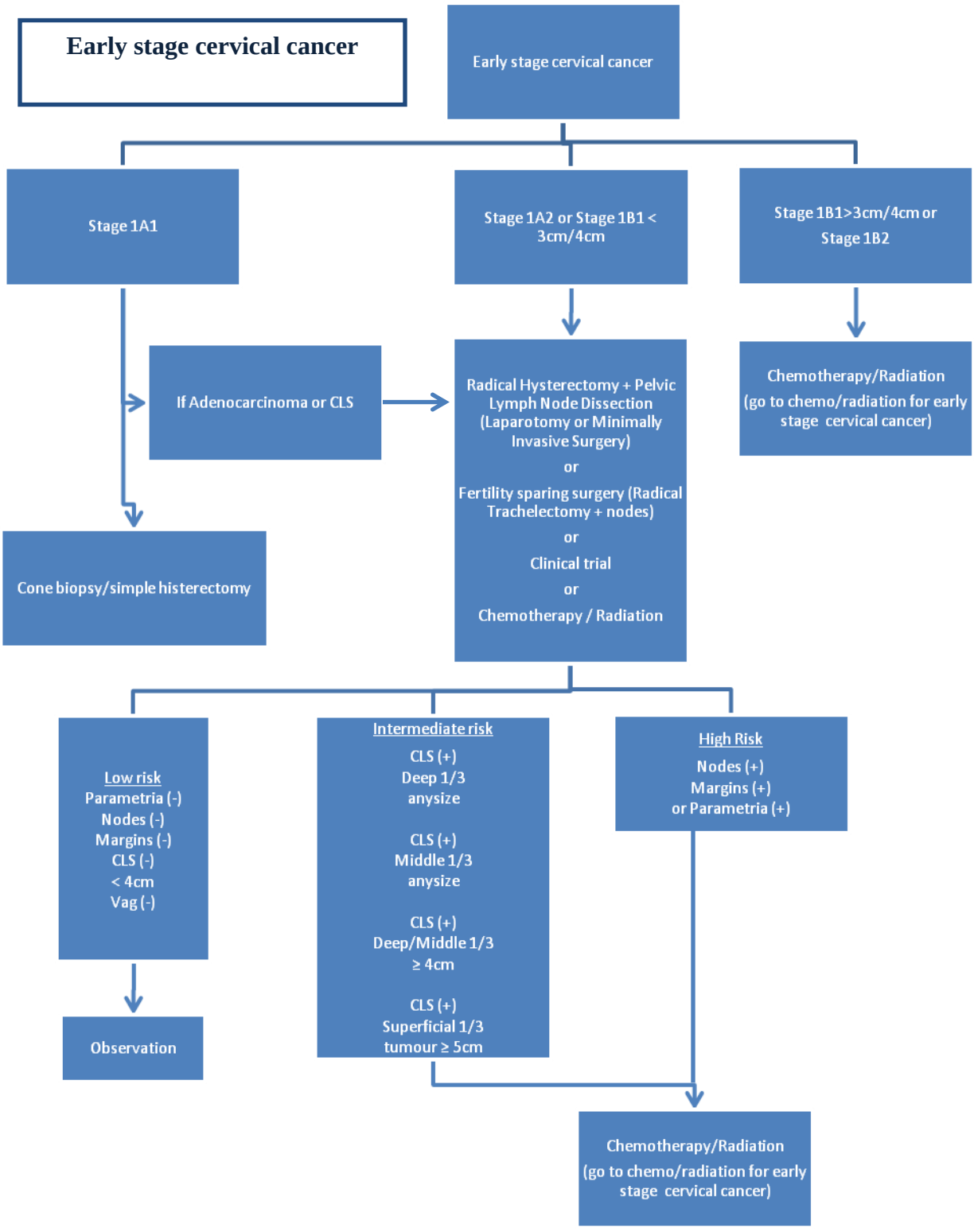
Expert pathology review

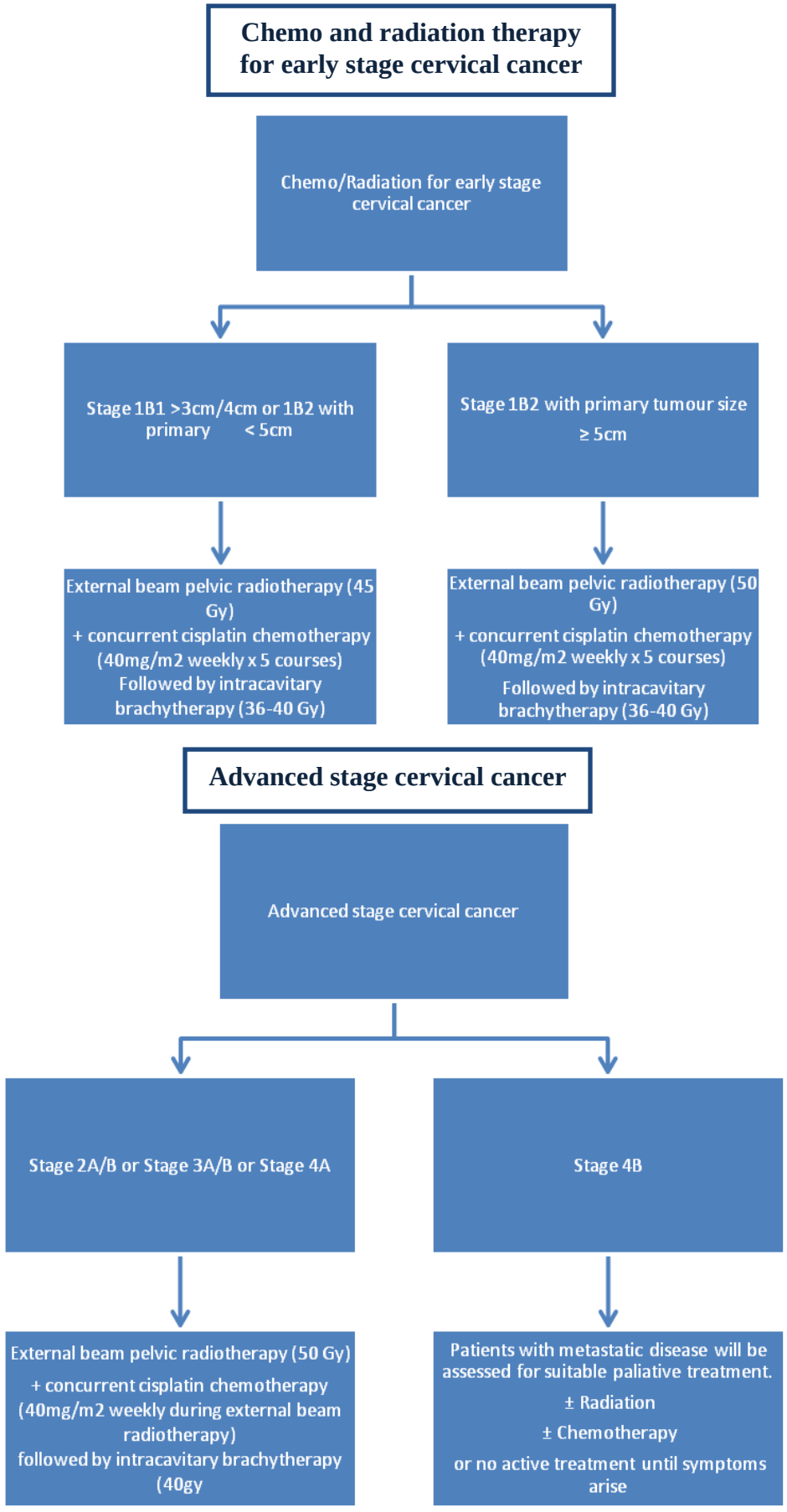
5. Pathology

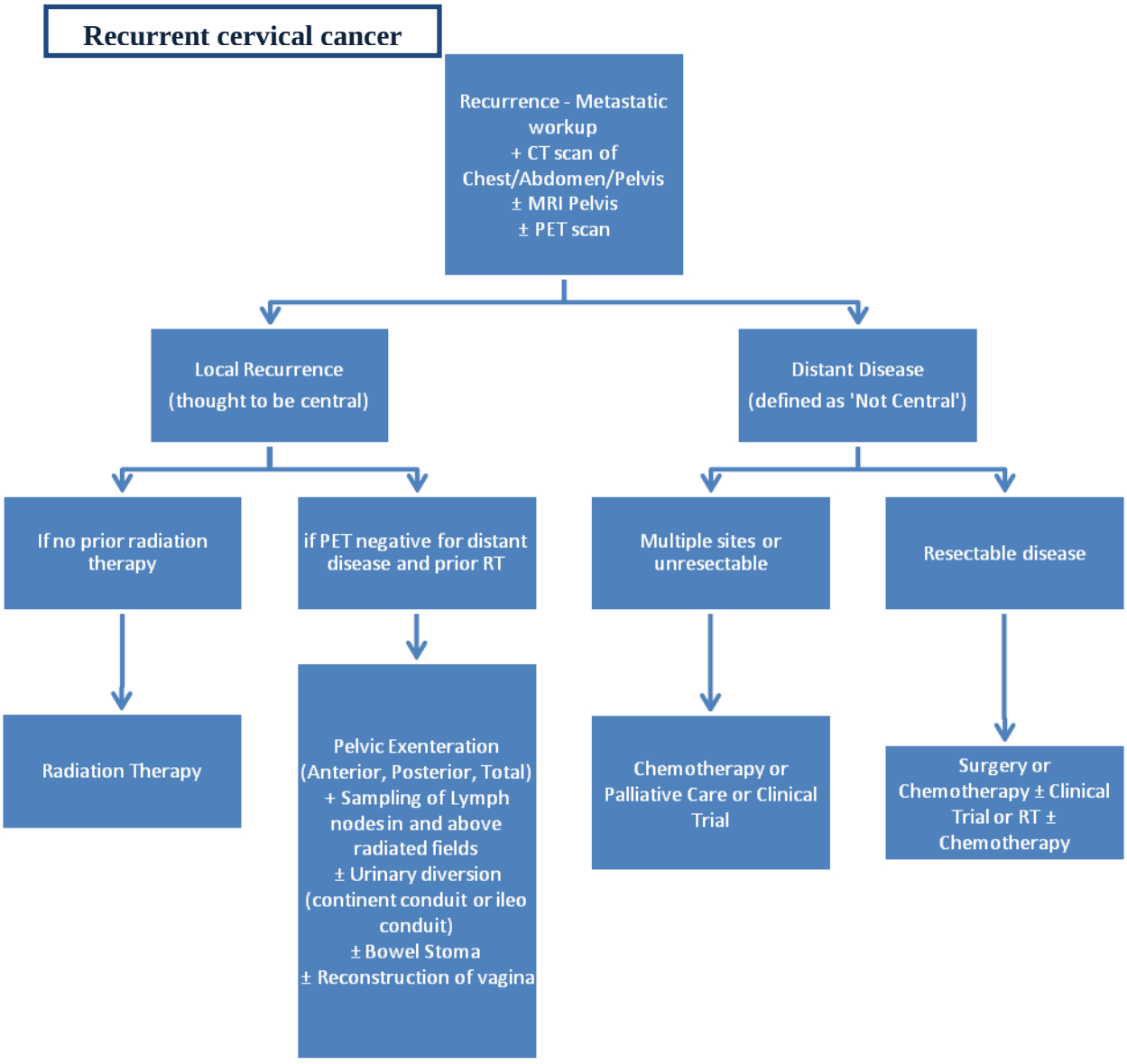
The human papillomavirus (HPV) is central to the development of cervical neoplasia and can be detected in 99.7% of cervical cancers. The most common histologic types of cervical cancer are squamous cell carcinoma, 69% and adenocarcinoma, 25%. Other rare histological types include serous, clear cell, endometrioid, small cell, undifferentiated and metastatic.

6. Management

6 Management Algorithms




Chemo and radiation therapy for early stage cervical cancer
Chemo/Radiation for early stage cervical cancer
Stage 1B1 >3cm/4cm or 1B2 with primary < 5cm
Stage 1B2 with primary tumour size ≥ 5cm
External beam pelvic radiotherapy (45 Gy) + concurrent cisplatin chemotherapy (40mg/m2 weekly x 5 courses) Followed by intracavitary brachytherapy (36-40 Gy)
External beam pelvic radiotherapy (50 Gy) + concurrent cisplatin chemotherapy (40mg/m2 weekly x 5 courses) Followed by intracavitary brachytherapy (36-40 Gy)
Advanced stage cervical cancer
Advanced stage cervical cancer
Stage 2A/B or Stage 3A/B or Stage 4A
Stage 4B
External beam pelvic radiotherapy (50 Gy) + concurrent cisplatin chemotherapy (40mg/m2 weekly during external beam radiotherapy) followed by intracavitary brachytherapy (40gy
Patients with metastatic disease will be assessed for suitable paliative treatment. ± Radiation ± Chemotherapy or no active treatment until symptoms arise


Recurrent cervical cancer
Recurrence - Metastatic workup
+ CT scan of Chest/Abdomen/Pelvis
± MRI Pelvis
± PET scan
Local Recurrence (thought to be central)
Distant Disease (defined as 'Not Central')
If no prior radiation therapy
if PET negative for distant disease and prior RT
Multiple sites or unresectable
Resectable disease
Radiation Therapy
Pelvic Exenteration (Anterior, Posterior, Total)
+ Sampling of Lymph nodes in and above radiated fields
± Urinary diversion (continent conduit or ileo conduit)
± Bowel Stoma
± Reconstruction of vagina
Chemotherapy or Palliative Care or Clinical Trial
Surgery or Chemotherapy ± Clinical Trial or RT ± Chemotherapy

6.2 Surgery

Radical Hysterectomy
Laparotomy or minimal invasive surgery: Surgery is aimed at removal of the uterus, parametria and paracervical tissue with an adequate vaginal cuff. In addition a bilateral pelvic lymphadenectomy is required. Removal of the tubes and ovaries will depend on patient's age and risk factors.

Identification of positive lymph nodes at radical hysterectomy: if the nodes and primary tumour can be removed with an adequate margin it is recommended to complete the radical hysterectomy. If the nodes cannot be removed, it is recommended to abandon the surgical procedure in favour of chemotherapy, EBRT and intracavitary radiation.

Fertility sparing surgery
A radical trachelectomy and pelvic lymph node dissection may be considered in women who wish to preserve their fertility and who present with a small tumor (<2cm) and a negative metastatic work up.

6.3 Chemotherapy

Weekly cisplatin in conjunction with radiation therapy (EBRT).

Early stage disease (Stage 1b1 and 1b2)
- Concurrent cisplatin chemotherapy 40 mg/m2 weekly x 5 courses

Locally advanced disease (Stage 2, 3, and 4a)
- Cisplatin chemotherapy (40mg/m2 weekly x 5 courses during external beam radiotherapy)
- Stage 4b - Patients with metastatic disease will be assessed for suitable palliative treatment. This may involve radiation, chemotherapy or, in some cases, no active treatment until symptoms arise.

6.4 Radiation Therapy

Used in conjunction with chemotherapy.

Early stage disease (< Stage 2)
- Stage 1b1 >3 cm or 1b2 with primary tumor size <5 cm – External beam pelvic radiotherapy (45 Gy) plus concurrent cisplatin chemotherapy, followed by intracavitary brachytherapy (36-40 Gy)
- Stage 1b2 with primary tumor size >5 cm – External beam pelvic radiotherapy (50 Gy) plus concurrent cisplatin chemotherapy, followed by intracavitary brachytherapy (36-40 Gy)

Advanced disease (Stage 2-4a)
- Stage 2a/b, 3a/b or 4a - External beam pelvic radiotherapy (50 Gy) plus concurrent cisplatin chemotherapy, followed by intracavitary brachytherapy (40 Gy)

- Stage 4b - Patients with metastatic disease will be assessed for suitable palliative treatment. This may involve radiation, chemotherapy or, in some cases, no active treatment until symptoms arise.

Post-op treatment for high risk tumors following Rad hyst and LND:
External beam chemo-radiation therapy (external beam pelvic radiation therapy to encompass the upper vagina, parametria, central pelvic tissues and lymph nodes, using a four field arrangement or IMRT) is recommended following modified radical hysterectomy and pelvic lymph node dissection for high risk features including: close or positive surgical resection margins, the presence of Capillary lymphatic invasion +/- high grade tumour and positive pelvic lymph nodes.

External Beam Radiotherapy

- Clinical target volume (CTV) includes the primary cervical tumour, upper vagina, parametrial, pelvic lymph nodes including the pre-sacral lymph nodes anterior to S1-S3, $\pm$ para-aortic lymph nodes
- CT plan
- Diagnostic or planning MRI to define posterior extension of disease
- Four coplanar pelvic fields for most patients
- AP-PA opposed pelvic fields if posterior extension of tumour, or para-aortic lymph nodes included in CTV
- 18 to 25 MV
- Pelvic dose: 45 Gy in 1.8 Gy daily fractions at ICRU reference point if primary tumour $\leq$5 cm in greatest size and no involved pelvic lymph nodes. Pelvic dose 50 Gy in 2 Gy daily fractions otherwise
- Para-aortic dose: 40 to 45 Gy in 1.8 to 2 Gy daily fractions
- Conformal shields to reduce the bowel, bladder and femoral head dose.

Intracavitary Brachytherapy

- Intrauterine line source 1-2 weeks after external radiotherapy (colpostats or ring optional)
- 36-40 Gy to an isodose 2 cm lateral to the applicator, remote afterloaded PDR brachytherapy, or
- 30 Gy in five fractions HDR brachytherapy beginning in the third or fourth week of external beam radiotherapy depending on tumor geometry. The external beam fraction is omitted on days when HDR is administered.

6.5 Oncology Nursing

Refer to general oncology nursing practices

7 Supportive Care

7.1 Patient Education

Cancer Care Ontario patient education link:
https://www.cancercare.on.ca/pcs/screening/cervscreening/patient_education/

Also refer to general patient education practices

7.2 Psychosocial Care

Refer to general psychosocial oncology care guidelines

7.3 Symptom Management

Refer to general symptom management care guidelines

7.4 Clinical Nutrition

Refer to general clinical nutrition care guidelines

7.5 Palliative Care

Refer to general oncology palliative care guidelines

8 Follow-up Care

Surgically treated patients:
Follow-up should be every 3-4 months for two years after surgery, then every 6 months for 3 years, then yearly. It should include a pap smear and pelvic examination. When indicated a CT scan of the abdomen and pelvis should be ordered. Hormone replacement therapy should be considered for patients who were pre-menopausal prior to treatment of cervical cancer and were rendered menopausal with surgery.

Radiation treated patients:
Every 3 to 4 months for 2 yrs after competing treatment, then every 6 months for 3 years.
MRI pelvis 6 months after completing treatment.
Cervical/vaginal cytology at the discretion of the oncologist beginning 1 year after competing RT.
Vaginal dilators for six months after the completion of brachytherapy to prevent vaginal stenosis. Some patients may require ongoing use of dilators.
Consider hormone replacement therapy for patients who were pre-menopausal prior to treatment for cervix cancer.

Recurrence:

Cervix cancers that recur centrally can be cured. All recurrences require metastatic workup including a CT scans of thorax, abdomen and pelvis, pelvic MRI.. When the recurrence is thought to be central, with no evidence of other disease, consider pelvic exenteration (anterior and/or posterior) . A PET scan can also be helpful to rule out distant metastatic disease.

At the time of exenterative surgery, efforts need to be made to rule out metastatic disease by sampling lymph nodes that are in and above the previously radiated fields. When disease is proven to be central and margins at resection can be cleared, this surgical procedure has the potential of curing 50-60% of those with a central recurrence.