INTRODUCTION:

Cervical cancer accounts for an estimated 12,000 new cases per year. Although the incidence of cervical cancer has been decreasing over the years, this disease still accounts for over 4,000 deaths.

The role of radiation therapy in the treatment of cervical cancer has been long established through clinical trial, providing strong evidence of support as an effective cervical cancer treatment. The traditional approach utilizes external beam irradiation therapy to the pelvis ± periaortic lymph nodes, as well as some form of brachytherapy boost, based on clinical and pathologic factors. There have been improvements in radiation therapy technology, reducing dose to normal surrounding tissue (bladder, rectum, and small bowel), but the majority of the experience to date is based on a point A dosing system. Concurrent chemoradiation therapy (cisplatin-based chemotherapy) is commonly used. This is based on multiple randomized clinical trials showing an improvement compared to radiation therapy alone.

GOAL OF THE GUIDELINE:

This guideline outlines several methods suitable for the employment of radiation therapy in conjunction with cervical cancer treatment. These include the use of three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), and internal radiation (brachytherapy). Although intensity modulated radiation therapy (IMRT) is becoming more widely available, the routine use in treating cervical cancer remains to be validated. Questions regarding the use of IMRT as an improvement over 3D conformal radiation therapy are currently being evaluated in several prospective multicenter clinical trials. Although there have been significant advances in imaging, planning and treatment delivery, this must be tailored to a thorough understanding to the stage of disease, pathways for dissemination and recurrence risk. Most external beam treatments are delivered using a high-energy linear accelerator. Brachytherapy is generally delivered as either low dose permanent implant or high dose rate implant. Principles of radiation therapy for these guidelines closely follow what is recommended both by the American Brachytherapy Society (Cervical Cancer Brachytherapy Task Group), as well as in National Comprehensive Cancer Network Practice Guidelines for Cervical Cancer.

GENERAL CONSIDERATIONS

Primary Treatment:
- Primary treatment for early stage cervical cancer is either radiation therapy or surgery. Inoperable stage IA patients may be treated with implant alone.
- Inoperable stage IB1 is typically treated with irradiation (external beam plus brachytherapy) ± concurrent chemotherapy.
- Concurrent chemoradiation is a primary treatment for patients with stage IB-IVA.

Adjuvant Treatment Following Radical Hysterectomy:
- Post-operative radiation therapy is typically not given for patients with stage IA-IIA disease after radical hysterectomy that are found to have negative nodes and no adverse risk factors (adverse risk factors are defined as a large primary tumor size, lymphvascular space invasion and/or deep stromal invasion).

Advanced Disease (stage IIB-IVA):
- Radiation treatment fields are determined by pelvic and/or para-aortic lymph node involvement.
- For patients without nodal disease (para-aortic or pelvic) or with disease noted to the pelvis, pelvic radiation therapy plus cisplatin-based chemotherapy and brachytherapy are recommended.
- For patients with positive para-aortic nodes (either by imaging or node dissection), should be considered for extended field radiation therapy plus cisplatin-based chemotherapy and brachytherapy.

Brachytherapy:
- Brachytherapy is an important component of radiation therapy delivery and typically performed with intrauterine tandem and vaginal colpostats, ring or cylinder.
- Brachytherapy is typically delivered towards the end or following external beam radiation therapy to allow for adequate tumor shrinkage.
- Types of brachytherapy utilized are either low dose rate or high dose rate implant. Low dose rate delivers 40-70 cGy per hour to point A for an additional dose delivered by external beam radiation therapy of 30-40 Gy to point A (for a cumulative dose of 80-85 Gy to point A). For high dose rate brachytherapy, commonly utilized dose fractionation is 6 Gy x 5 insertions, for a total brachytherapy dose of 30 Gy (equivalent of 40 Gy to point A using low dose rate brachytherapy)

Treatment Planning:
- CT-based simulation is considered standard of care. MRI and PET imaging is useful to determine soft tissue/perimetrial involvement and nodal volume coverage, respectively. Microscopic nodal disease requires a dose of 45 Gy at 1.8-2 Gy per fraction. An additional 10-15 Gy may be used to boost areas of gross unresected lymph node in a highly conformal approach.

Chemotherapy:
- Concurrent cisplatin-based chemotherapy is typically given to the majority of patients treated definitively with radiation therapy.
MEDICALLY NECESSARY INDICATIONS FOR RADIATION THERAPY AND TREATMENT OPTIONS:

Definitive/Preoperative Radiation Therapy

- Stage IA – IA2 – Brachytherapy (LDR or HDR) +/- 2D/3D-CRT (40-50 Gy; 28 fx max)
- Stage IB1 – Pelvic 2D/3D-CRT (40-50 Gy; 28 fx max) + brachytherapy boost
- Stage IB2-IIA – Pelvic radiation therapy 2D/3D-CRT (40-50 Gy; 28 fx max) + brachytherapy boost and concomitant chemotherapy +/- adjuvant hysterectomy.
- Stage IIB-IVA – Pelvic and/or paraortic 2D/3D-CRT + brachytherapy + concurrent chemotherapy.
- Stage IVB – 2D/3D-CRT +/- brachytherapy for palliation only (symptom control)

- **Grossly involved unresected nodes may be evaluated for boosting with an additional 10-15 Gy**

Postoperative (Adjuvant) Radiation Therapy

- Patients found to have deep cervical stromal invasion, lymphovascular invasion and/or bulky primary tumors.
- Pelvic 2D/3D-CRT (45-50 Gy; 28 fx max) +/- concurrent chemotherapy
- Patients with positive nodes, positive margins and/or parametrial invasion –
- Pelvic 2D/3D-CRT (45-50 Gy; 28 fx max) +/ concurrent chemotherapy
- Pelvic 2D/3D-CRT (45-50 Gy; 28 fx max) +/- vaginal brachytherapy boost (LDR or HDR) can be considered in women with a positive margin.

Local /Regional Recurrence

- No previous RT or outside previous RT fields
  - 2D/3D-CRT + chemotherapy +/- brachytherapy
- Previous RT
  - Intraoperative Radiation Therapy (IORT) for centralized disease
  - Possible Brachytherapy (LDR or HDR) for centralized disease < 2cm Tumor directed 2D/3D-CRT +/- chemotherapy if noncentral disease

  **Grossly involved unresected nodes may be evaluated for boosting with an additional 10-15 Gy**

**Unless otherwise indicated standard radiation fractionation consists of 1.8 Gy to 2.0 Gy per day**

TREATMENT OPTIONS REQUIRING ADDITIONAL CLINICAL REVIEW:

Intensity modulated radiation therapy (IMRT)
IMRT is not indicated as a standard treatment option and should not be used routinely for the delivery of radiation therapy for cervical cancer. IMRT is strictly defined by the utilization of inverse planning modulation techniques. IMRT may be appropriate for limited circumstances in which radiation therapy is indicated and 3D conformal radiation therapy (3D-CRT) techniques cannot adequately deliver the radiation prescription without exceeding normal tissue radiation tolerance, the delivery is anticipated to contribute to potential late toxicity or tumor volume dose heterogeneity is such that unacceptable hot or cold spots are created.

Clinical rationale and documentation for performing IMRT rather than 2D or 3D-CRT treatment planning and delivery will need to:

- Demonstrate how 3D-CRT isodose planning cannot produce a satisfactory treatment plan (as stated above) via the use of patient specific dose volume histograms and isodose plans.

- Provide tissue constraints for both the target and affected critical structures.

**Stereotactic Body Radiation Therapy (SBRT)**
Stereotactic Body Radiation Therapy is not a standard treatment option for the treatment of cervical cancer.

**Proton Beam Radiation Therapy**
Proton beam is not an approved treatment option for cervical cancer. Proton beam has not been proven superior treatment to conventional radiation therapy.
REFERENCES


