Taipei Veterans General Hospital Practices Guidelines Oncology

Cervical Cancer

2022.05.23修訂

General Radiation Information

General Radiation Information

- Treatment recommendations should be made after joint consultation and/or discussion by a multidisciplinary team including gynecologist, radiation oncologists, medical oncologists, radiologists, and pathologists.
- Initial Hb, SCC levels, PV&PR Exam, pathology, CT and/or MR scans, PET scan, whole body bone scan reports, when available, should be reviewed by the multidisciplinary team. This will allow an informed determination of treatment volume and field borders prior to simulation.
- MRI is the best imaging modality for determining soft tissue and parametrial involvement in patients with advanced tumors. In patients who are not surgically staged, PET imaging is useful to help define the nodal volume of coverage, and may be useful postoperatively to confirm removal of abnormal nodes.
- Brachytherapy is a critical component of definitive therapy for all patients with primary cervical cancer who are not candidates for surgery. This is performed using an intracavity and /or an interstitial approach.
- Optimal results are achieved when whole course of radiotherapy is completed within 8 weeks.

General Radiation Information

Simulation

- Immobilization device is strongly recommended for reproducibility of daily set-up
- The customized immobilization device for both knee and foot is applied in the supine position.
- CT simulation and 3D/ IMRT/ VMAT/ Tomotherapy treatment planning is necessary.

  A treatment planning CT scan is performed using 5-mm slices. The CT scans were obtained from at least the T12-L1 vertebral body to 5 cm below the ischial tuberosities. All patients has a full bladder and empty rectum during scanning and simulation. During daily treatment they are instructed to have a full bladder.

***Radiation technique*:**

- 3D-CRT or IMRT/ VMAT/ Tomotherapy (+/-simultaneous integrated boost (SIB))
- Adaptive RT: re-simulation every 10-14 day during EBRT.

Principle of Target volume delineation

Definitions of target volumes and critical structures

- Following the International Commission on Radiation Units and Measurements ICRU 62 recommendations, a CTV was delineated on individual axial CT slices in all patients by our radiation oncologist.

Gross Target Volume (GTV) delineation

- Target volume delineation based on CT simulation images. Diagnostic CT/MR reports, and PET/CT scans should be reviewed, when available, for precise delineation of GTV.

Clinical Target Volume (CTV) delineation

- The clinical target volume should include GTV and the areas at risk for microscopic disease.

Definitive radiotherapy:

- CTV_H: GTV of primary tumor and lymphadenopathy
- CTV_L:

  a. GTV + parametria + uterosacral ligaments + upper vagina (3-4 cm) + pelvic LNs + presacral LNs for pelvic radiotherapy

  b. GTV + parametria + uterosacral ligaments + upper vagina (3-4 cm) + pelvic LNs + presacral LNs + paraaortic LNs for extended field radiotherapy

- The final target volume should consider the relative risk of nodal metastases at specific nodal location is depended on the site of the origin of primary tumor (e.g. perirectal LNs for tumor invading rectum, inguinal LNs for tumor invading lower third vagina).
- Pelvic LNs:

  a. For patients with negative nodes at surgical or radiology imaging, Entirety external iliac, internal iliac and obturator nodal basin should be included.

  b. For patients with higher nodal involvement risk (e.g. bulky tumor, suspected or confirmed nodes confined to the low true pelvis), common iliac should be covered as well.
- For patients with documented common iliac and/or para-aortic nodal involvement, extended field radiotherapy with up to renal vessels or even higher are recommended.
- For patients with L/3 vagina involvement, bilateral inguinal LN area radiotherapy should be included.

Principle of Target volume delineation

Clinical Target Volume (CTV) delineation (continued)

Postoperative radiotherapy:

- CTV:
  a. Upper 3-4 cm of vaginal cuff + parametria + pelvic LNs + presacral LNs for pelvic radiotherapy
  b. Upper 3-4 cm of vaginal cuff + parametria + pelvic LNs + presacral LNs + paraaortic LNs for extended field radiotherapy
  c. An additional boost to grossly involved unresected nodes may be considered.

Planning Target Volume (PTV) delineation

- The margins of PTV should consider *internal organ motion* and *setup errors*
- For single-phase CT simulation, the recommended margins to compensate organ motions (without IGRT) are as follows:
  PTV = CTV + 5-10mm in all directions

Field margins for box 4-fields technique

- The anterior field margins: possible extensions of the tumor into the body of the uterus.
- The posterior field margins: tumor extension into the uterosacral ligament and presacral lymph nodes.
- Lateral field margins: include the pelvic lymph nodes.
- For lesions in the lower one third of the vagina, the inguinal lymph nodes need to be treated.
- Extended-field radiation to treat occult or macroscopic para-aortic lymph node disease needs to be carefully planned to ensure adequate dose (45-50.4 Gy, 1.8-2.0 Gy/ Fx/ day for microscopic disease) without exceeding bowel, spinal cord, or renal tolerances.

Principle of Target volume delineation

Radiation dose

- Definitive radiotherapy:
  a. 45 –50.4 Gy, 1.8-2.0 Gy/ Fx/ day to CTV_L + brachytherapy total dose ≥ 80Gy for small-volume tumor or total dose ≥ 85 Gy for large-volume tumor (LDR equivalent or EQD2)
  b. 45-50.4 Gy, 1.8-2.0 Gy/ Fx/ day to CTV_L, SIB with 61.6 Gy, 2.2 Gy/Fx to CTV-H + brachytherapy total dose ≥ 80 Gy for small-volume tumor or total dose ≥ 85 Gy for large-volume tumor (LDR equivalent or EQD2)
  c. 45 –50.4 Gy, 1.8-2.0 Gy/ Fx/ day to CTV_L, small field tumor boost up to 70.4 Gy (for poor response tumor and/or lymphoadenopathy) + brachytherapy total dose ≥ 80 Gy for small-volume tumor or total dose ≥ 85 Gy for large-volume tumor (LDR equivalent or EQD2)

- Post-operative radiotherapy:
  a. 45 – 50.4 Gy (+ Brachytherapy as IVRT for high risk including close or positive vaginal margin)
  b. Additional 10 - 20 Gy boost with SIB technique to grossly involved unresected nodes if needed

SEDLIS CRITERIA FOR EXTERNAL PELVIC RADIATION AFTER RADICAL HYSTERECTOMY IN NODE-NEGATIVE, MARGIN-NEGATIVE, PARAMETRIA-NEGATIVE

LVSI	Stromal Invasion	Tumor Size (cm) (Determined by clinical palpation)
+	Deep 1/3	Any
+	Middle 1/3	≥2
+	Superficial 1/3	≥5
-	Middle or Deep 1/3	≥4

LVSI: Lymphovascular space invasion

Sedlis criteria often simplified to needing 2 or more of these factors:

- LVSI involvement
- Deep stromal invasion (middle or deep third); [i.e >1/3 stromal invasion]
- Size > 4 cm

1 Modified with permission from 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 study group. Gynecol Oncol 1999:73:177-183 https://pubmed.ncbi.nlm.nih.gov/10329031/

2 Delgado G, Bundy B, Zaino R, et al. Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol 1990:38:352-357. https://pubmed.ncbi.nlm.nih.gov/2227547/

3 Rotman M. Sedlis A, Piedmont MR, 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 2006,65:169-176. https://pubmed.ncbi.nlm.nih.gov/16427212/

Brachytherapy

Postoperative RT

– Vaginal brachytherapy with 11- 20 Gy / 2- 4 Fx to 0.5 cm submucosa, 3.0-4.0 cm active length is recommended for high risk but negative margin patient. Higher dose is also recommended for positive margin patient.

Definitive RT

– Intracavitary or interstitial brachytherapy techniques have proven to be a vital component in treatment of invasive cervical tumors. This is particularly true for more advanced stages of disease.

– Initial radiation treatment of 45-50.4 Gy/ 25-28 Fx to the whole pelvis is often necessary to obtain tumor shrinkage to permit optimal intracavitary placements.

Point A dose calculate plan (brachytherapy + EBRT)

- for small tumors: at least 80 Gy (LDR equivalent)
- for larger tumors: at least 85 Gy (LDR equivalent)

– However, limitations of the point A dosing system does not take into account the 3D shape of tumor or normal tissue structure correlations. Evidence showed that image–guided brachytherapy improves outcomes and decreases toxicity. An MRI prior to brachytherapy can help guide therapy.

Brachytherapy

Definitive RT (continued)

3D dose calculate plan (image –guided brachytherapy + EBRT)

- IR-CTV (intermediate-risk clinical tumor volume) :

  cover the initial tumor volume at the time at diagnosis: EQD2 ≥ 60 Gy

  * EQD2 : equivalent dose in 2 Gy per fraction
  * EQD2 to the tumor using α/β=10 Gy, and EQD2 to the organ at risk α/β=3 Gy
  * If the patient has already received EBRT EQD2 ≥ 60 Gy, IR-CTV could be omitted

- HR-CTV (high-risk clinical tumor volume) :

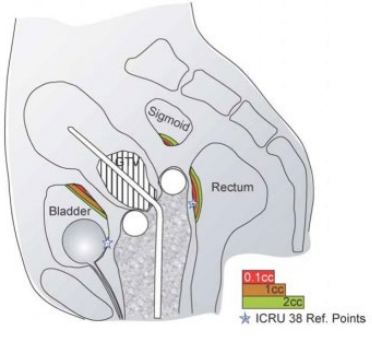
  cover the tumor volume plus whole cervix at brachytherapy

  - for residual tumors < 4cm: D90 ≥ 80 Gy (EQD2)
  - for residual tumors > 4cm : D90 ≥ 85 Gy (EQD2) (≥ 87 Gy is preferred)

  * If CT anatomy dose not permit identification of the cervix, a height of approximately 3 cm should be contoured for the cervix
  * D90 : the dose received by 90% of the volume

- Normal tissue should be limited according to:

  - D_{2cc} rectal dose: EQD2≤ 65-75 Gy
  - D_{2cc} sigmoid colon dose: EQD2 ≤ 70-75 Gy
  - D_{2cc} bladder dose: EQD2 ≤ 80-90 Gy



  * D_{2cc} : the minimum dose in the most irradiated 2 cm^3 normal tissue volume
  * The above normal tissue dose is suggested by NCCN guideline. However, if it is more crucial to consider the tumor coverage, the dose limits of normal tissue could be adjusted depending on physician's decision.

Non-brachytherapy alternatives

Situations when intracavitary brachytherapy cannot be performed

- Medically unfit for brachytherapy
- Patient refusal of brachytherapy
- Inability of tandem insertion (vaginal stenosis, uterine malformations)
- Insufficient reduction of the tumor volume after EBRT
- Asymmetric tumors

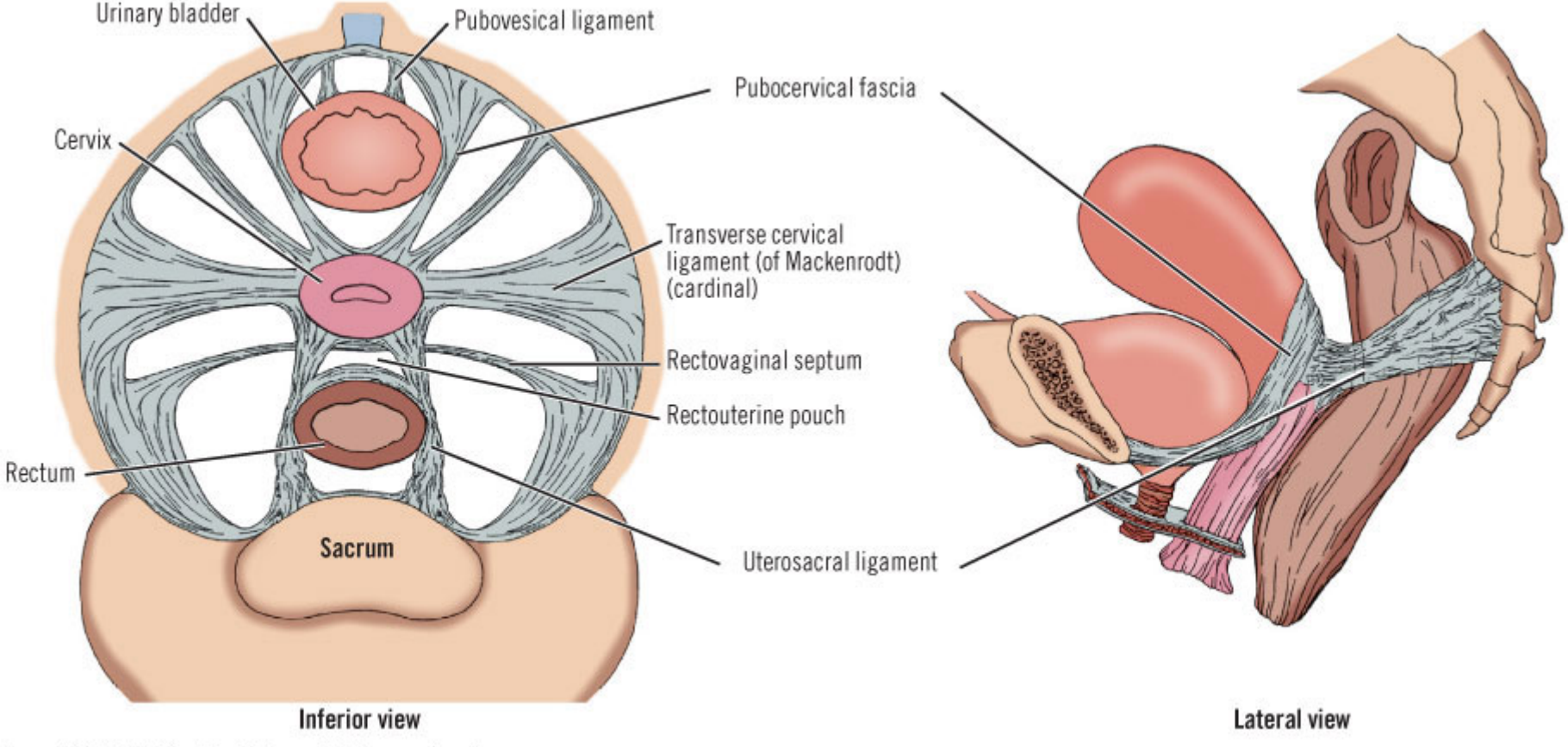
Alternative treatments

- EBRT
  - SIB technique or sequential boost to cervical tumor after pelvic irradiation
  - Dose : D90 to cervical tumor ≥ 80 Gy (EQD2)
- Carbon-ion radiation therapy may be considered
  - Indication :
    - FIGO stage II-IVA squamous cell carcinoma, ≥ 6 cm
    - FIGO stage II-IVA adenocarcinoma

Intraoperative Radiation Therapy (IORT)

IORT is a specialized technique that delivers a single, highly focused dose of radiation to an at-risk tumor bed or isolated unresectable residual disease during an open surgical procedure. It is particularly useful in patients with recurrent disease within a previously radiated volume. During IORT, overlying normal tissue (such as bowel or other viscera) can be manually displaced from the region at risk. IORT is typically delivered with electrons using preformed applicators of variable sizes matched to the surgically defined region at risk, which further constrains the area and depth of radiation exposure to avoid surrounding normal structures.

Anatomy Reference



Acronym

- 3D-CRT: 3D Conformal Radiation Therapy
- CCRT: Concurrent chemoradiotherapy
- CT: computed tomography
- CTV: Clinical Target Volume
- EBRT: External Beam Radiation Therapy
- Fx: fraction
- GTV: Gross Tumor Volume
- HDR: High dose rate
- IGRT: Image-Guided Radiation Therapy
- IMRT: Intensity Modulated Radiation Therapy
- VMAT: Volumetric-modulated Arc Therapy
- LDR: Low dose rate
- MRI: Magnetic Resonance Image
- PET: Positron Emission Tomography
- PTV: Planning Target Volume
- RT: Radiation Therapy
- IR-CTV: intermittent risk CTV
- HR-CTV: High risk CTV
- SBRT: Stereotactic Body Radiation Therapy

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