RADIOTHERAPY IN CERVICAL CARCINOMA

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Abstract

Cervical cancer is one of the most common cancers in females in developing countries. Radiation therapy plays a major role in the treatment of early and advanced stages. Concurrent chemoradiation has improved treatment outcome in locally advanced cervical cancer. The implementation of intensity-modulated radiotherapy (IMRT) and image-guided brachytherapy (IGBT) is waiting to be proved. Chiang Mai Medical Journal 2009;48(4):125-133.

Keywords: radiotherapy, cervical carcinoma

Cervical cancer is one of the most common female cancers in Thailand and many developing countries, with an incidence of 24.5/100,000.(1) The treatment of cervical cancer depends on the stage of disease. The treatment of cervical carcinoma is shown in Table 1.

Role of radiation therapy in cervical cancer

In the early stage (stage I-IIA by FIGO staging), the roles of radiotherapy are post-operative radiotherapy, and radical treatment when a patient has inoperable status.(2) In the advanced stage (stage IIB-IVA by FIGO staging), concurrent chemo-radiation with a cisplatin-based regimen is standard.(3-7)

Radio-therapeutic management in cervical cancer is composed of external beam radiotherapy (EBRT) and brachytherapy (BT). EBRT is the use of a high energy photon, which irradiates from outside to the tumor, while BT is an application of the radioisotope source, close or inside the tumor. In the treatment of cervical cancer, radiation oncologists use both methods in giving irradiation to a patient, with the goal of increasing radiation dose to the tumor and decreasing it to normal tissue (bladder and rectum). Moreover, in a pos-
operative setting, post-operative radiotherapy is indicated as follows:(8)

- Major risks: positive margin (surgical margin, vaginal margin or parametrial margin), positive lymph node.
- Minor risks: size > 4 cm, lymphovascular invasion (LVSI), deep stromal invasion.

If patients have one major risk or two minor risks, postoperative radiotherapy would be prescribed. Concurrent chemo-radiation is recommended in a major risk indication.

**Treatment fields of EBRT** (9)

Whole pelvic radiotherapy: two or four-field box technique

Antero-posterior (AP) field & Postero-anterior (PA) field
- Upper border: L4-L5 interspace
- Lower border: Obturator foramina
- Lateral border: 1.5-2 cm outer pelvic rim
- Lateral field (in the case of the four-field box technique)
  - Upper and lower border: the same as the AP & PA field
  - Anterior border: cover pubic symphysis
  - Posterior border: S2-S3 interspace

The prescribed dose of post-operative setting depends on pathological status. Normally, the dose of EBRT is prescribed in conventional fractionation (1.8-2.0 Gray per fraction, five fractions per week) to the total dose of 45-50 Gray. If the pathological status shows a close or positive margin at the parametrial side, an additional boost can be prescribed to 56-60 Gray in conventional fractionation.

Brachytherapy was designed to increase the dose to the tumor, while decreasing it to normal tissue. According to dose rate, brachytherapy was divided into a Low Dose Rate (LDR; less than 2 Gy/hour) and High Dose Rate (HDR; more than 12 Gy/hour). Nowadays, HDR with remote afterloading can be used to avoid radiation exposure to the officers, lessen hospitalization and allow optimization.(10) Therefore, HDR is commonly used in Thailand.

In the patient whose pathologic results show positive vaginal margin, intracavitary brachytherapy is applied to the vaginal stump to increase the tumoricidal dose. The dose schedule is performed depending on the treatment center, and the volume of treatment depends on disease status. Two colpostats or vaginal cylinders are used to treat the disease in the vaginal stump and its vaginal involvement. The American Brachytherapy Society (ABS) recommendations were published in the year 2000 to guide the dose schedule in treatment of cervical cancer.(11)

In a medically inoperable setting, radical radiotherapy alone is applied. The treatment schedule is composed of EBRT plus BT. The dose of 45-50 Gy in conventional fractionation is applied in whole pelvis irradiation, while early central shielding reduces the dose to the bladder and rectum.(11)
BT is used to increase the dose to the tumor and reduce it to normal tissue. The dose schedule in early-stage cervical cancer as well as our dose schedule is shown in Table 2.

Radiotherapy of locally advanced cervical carcinoma

The treatment of locally advanced cervical cancer is concurrent chemo-radiation with a cisplatin-based regimen.\(^{(3-7)}\) In the radiotherapeutic aspect, the treatment schedule is composed of EBRT plus BT. The dose of 45-50 Gy in conventional fractionation is applied to cover microscopic disease, and an additional boost of 5-10 Gy to the parametrial is added to increase the dose to macroscopic disease in the parametrium or pelvic side wall (stage IIB-IIIB). Supporting data of cisplatin-based chemoradiation in locally advanced cervical cancer are shown in Table 3.

BT is used for escalating the dose to a primary tumor at a curative level (85-90 Gy), while it spares the dose to normal organ tissue (bladder and rectum). Intracavitary brachytherapy is most commonly used as treatment. Interstitial brachytherapy is used when the tumour has bulky parametrial invasion, bulky primary disease, narrow vagina or poor geometry, and a suboptimal dose distribution of intracavitary brachytherapy is utilized.\(^{(12)}\)

The ABS dose schedule of the treatment in locally advanced cervical carcinoma is shown in Table 4.

### Prescription point of ICBT

The prescription point of brachytherapy is identified by orthogonal x-ray and divided to the two main categories as follows:\(^{(13)}\)

1. The dose of brachytherapy is prescribed at point A and B, which have the following definitions;
   - Point A: 2 cm lateral to the midline, and 2 cm above the surface of the ovoid in the lateral vaginal fornix.
   - Point B: 3 cm lateral to point A.

2. According to the International Commission on Radiological Unit and Measurement (ICRU), the dose of normal tissue is evaluated from the bladder and rectum points, which have definitions the following;
   - ICRU bladder reference point, which is at the inferior part of the bladder catheter balloon.
   - ICRU rectal reference point, which is on the anterior rectal wall at a point perpendicular from the cervical os or lowest vaginal source.

Generally, the dose at ICRU points should be less than 80% of point A.

### Table 2. The dose schedule of radiotherapy in early stage cervical cancer form ABS recommendations.

<table>
<thead>
<tr>
<th>Studies</th>
<th>EBRT dose (Gy)</th>
<th>BT dose</th>
<th>No. of HDR fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABS recommendations</td>
<td>20</td>
<td>7.5</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>6.5</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>6.0</td>
<td>8</td>
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<tr>
<td></td>
<td>45</td>
<td>6.0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>5.3</td>
<td>6</td>
</tr>
<tr>
<td>Chiang Mai schedule</td>
<td>50</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>
**Table 3.** The studies that showed concurrent chemo-radiation benefit in locally advanced cervical cancer.

<table>
<thead>
<tr>
<th>Refs</th>
<th>Study</th>
<th>FIGO</th>
<th>Pts in arms</th>
<th>RT regimen</th>
<th>Chemo regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whitney, et al. (3)</td>
<td>GOG 85/SWOG 8695</td>
<td>IIB-IVA</td>
<td>177</td>
<td>Pelvic EBRT/IC</td>
<td>Cis/5Fu/HU</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>191</td>
<td>Pelvic EBRT/IC</td>
<td></td>
</tr>
<tr>
<td>Morris, et al. (4)</td>
<td>RTOG 9001</td>
<td>IB2-IVA*</td>
<td>195</td>
<td>Pelvic EBRT/IC</td>
<td>Cis/5Fu/none</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>193</td>
<td>Pelvic EBRT/IC</td>
<td></td>
</tr>
<tr>
<td>Rose, et al. (5)</td>
<td>GOG 120</td>
<td>IIB-IVA</td>
<td>177</td>
<td>Pelvic EBRT/IC</td>
<td>Weekly cis Cis/5Fu/HU none</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>173</td>
<td>Pelvic EBRT/IC</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>176</td>
<td>Pelvic EBRT/IC</td>
<td></td>
</tr>
<tr>
<td>Peters, et al. (6)</td>
<td>GOG 109/SWOG 8797/RTOG 9112</td>
<td>IA2-IIA</td>
<td>127</td>
<td>Pelvic EBRT/IC</td>
<td>Cis/5Fu/none</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>116</td>
<td>Pelvic EBRT/IC</td>
<td></td>
</tr>
<tr>
<td>Keys, et al. (7)</td>
<td>GOG 123</td>
<td>IB2‡</td>
<td>183</td>
<td>Pelvic EBRT/IC</td>
<td>Weekly cis Cis/5Fu/none</td>
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<td></td>
<td></td>
<td></td>
<td>186</td>
<td>Pelvic EBRT/IC</td>
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</table>

**Table 4.** The dose schedule in locally advanced cervical cancer.

<table>
<thead>
<tr>
<th>Studies</th>
<th>EBRT dose (Gy)</th>
<th>BT dose (Gy)</th>
<th>No. of HDR fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABS recommendations (3)</td>
<td>45</td>
<td>6.5</td>
<td>5</td>
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<tr>
<td></td>
<td>45</td>
<td>5.8</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>50.4</td>
<td>7.0</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>50.4</td>
<td>6.0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>50.4</td>
<td>5.3</td>
<td>6</td>
</tr>
<tr>
<td>Our schedule</td>
<td>56</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

**Radiation therapy in recurrent disease**

Patients with an isolated pelvic recurrence after initial treatment with radical hysterectomy can sometimes be treated with radiation therapy. Those who have isolated central recurrence without regional disease can be handled in up to 60-70% of cases by EBRT plus BT. The prognosis is poorer when the pelvic wall is involved and only 10-20% of patients survive 5 years after radiation therapy. Pelvic exenteration is the treatment of choice in patients who experience local recurrence after radical radiotherapy and have a 5-year over-all survival rate of approximating 50 percent. Re-irradiation in patients who were previously irradiated is
Radiotherapy in cervical carcinoma

Radiotherapy in cervical carcinoma is a serious issue. Normally, this is considered in the case of inoperable recurrence. However, the dose of previous irradiation, late complication status and patient issue should be carefully considered before decision making. More recent experiences have provided encouraging results in selectively re-irradiated patients with small central recurrences, in whom the use of brachytherapy was emphasized. Despite these advances, a higher complication rate than that seen with primary radiation is to be expected, and patients have to be appropriately counseled prior to re-irradiation.\(^{(16)}\)

Radiation therapy in palliative treatment of cervical cancer

In the case of metastatic disease, and poor performance status that is not ready for radical treatment, radiotherapy can be used as a palliative goal to relieve symptoms (for example; bleeding, pain and respiratory obstruction) at the site of the lesion. The dose of 3-10 Gy per fraction is prescribed with this intention. EBRT or Brachytherapy can be used according to the disease and physician’s opinion.\(^{(17)}\)

Results of treatment

The treatment of cervical cancer with radiotherapy is dependent on the size of tumor, and stage and performance status of the patient. The results of overall treatment and brachytherapy are shown in Table 5 and Table 6, respectively.

Complications

The development of complications depends on multiple factors (age, performance status, co-morbidities, dose of EBRT and the use of chemotherapy). Complications directly attributable to brachytherapy relate to the very high dose delivered around the cervix, upper vagina, bladder base and anterior rectal wall. The pattern of care study reported that 8-15% of cervical cancer patients, who were treated with radical radiotherapy, required hospitalization due to severe complications.\(^{(25)}\) These may be considered as follows:

- Vaginal side effects predominantly relate to stenosis and shortening of the vagina, which can be prevented to some degree by the use of vaginal dilators.
- Rectal complications are compounded by the external beam dose delivered and include rectal frequency and bleeding due to telangiectasia. Severe rectal problems should be seen in no more than 5% of patients, but less troublesome grade I and II side effects are seen in over 30%.
- Bladder side effects include frequency and hematuria from bladder telangiectasia. Occasionally, urethral stricture may also develop requiring dilation. These are typically seen in less than 5% of patients.

Normally, rectal complications develop sooner than bladder complications, with the mean time to onset for rectal complications

<table>
<thead>
<tr>
<th>Stage</th>
<th>5 yr survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA1</td>
<td>&gt;95</td>
</tr>
<tr>
<td>IA1, IA2</td>
<td>&gt;95</td>
</tr>
<tr>
<td>IB1</td>
<td>80-90</td>
</tr>
<tr>
<td>IB2, IIA</td>
<td>80</td>
</tr>
<tr>
<td>IIB</td>
<td>65-75</td>
</tr>
<tr>
<td>III</td>
<td>30-50</td>
</tr>
<tr>
<td>IVA</td>
<td>10-20</td>
</tr>
<tr>
<td>IVB</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

Table 5. The overall treatment results of cervical cancer.\(^{(2)}\)
being two to three years, and bladder problems developing a year or two later on average.\(^{(26)}\)

**Development of radiotherapy in cervical cancer**

Nowadays, with new imaging and machines, the development of EBRT and BT has been shifted into image-based treatment planning. In EBRT, the treatment with Intensity-Modulated Radiotherapy (IMRT) has been developed to replace conventional whole pelvic radiotherapy (WPRT). Many pilot studies have show the benefit of IMRT in decreasing organ risk doses in the treatment of cervical cancer.\(^{(27,28)}\) However, the benefits of IMRT are controversial.\(^{(29)}\)

The treatment of cervical cancer has developed to image-based brachytherapy. With the emergence of recommendations from the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) in the year 2005, volume-based parameters have been used in many studies.\(^{(30)}\) Studies from Vienna, Paris and Leuven showed the benefit of magnetic resonance image (MRI)-guided brachytherapy in the treatment of cervical cancer.\(^{(31)}\) In the year of 2007, the study of the clinical impact of MRI-guided brachytherapy was published.\(^{(32)}\) The development of image-based brachytherapy still waits for further study to confirm clinical benefits.

**References**

Radiotherapy in cervical carcinoma


เรื่องรักษาในมะเร็งปากมดลูก

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พิมพ์ชัย ภัททิศภูทะ, พ.บ., อิ่มใจ ชิตาภัณฑ์, พ.บ.

หัวข้อเรื่องรักษาและมะเร็งด้วยการรักษาคุณภาพและการรักษาแบบแผนคุณภาพ มหาวิทยาลัยเชียงใหม่

บทคัดย่อ
มะเร็งปากมดลูกเป็นมะเร็งที่พบบ่อยในประชากรสตรีในประเทศกำลังพัฒนา รังสีรักษาเป็นการรักษาหลักอย่างหนึ่งในการรักษามะเร็งปากมดลูก ทั้งในระยะเริ่มต้นและระยะลุกลาม ในปัจจุบัน รังสีดิจิตอลนิวโคมม์ได้กลายเป็นการรักษาหลักในการรักษามะเร็งปากมดลูกระยะลุกลาม การพัฒนาของเทคโนโลยีทางด้านรังสีรักษา อาทิเช่น รังสีแปรความเข้มสามมิติ หรือการใช้ภาพทางการแพทย์ร่วมรักษาในรังสีรักษาระยะใกล้ลักษณะ ได้รับการพัฒนาและตรวจสอบ เพื่อนำมาใช้ในการรักษา เชิงใหม่ เวชสาร 2552;48(4):125-133.

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