Current Status of Image Guided Brachytherapy for Cervical Cancer In Japan

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Director of Heavy Ion Medical Research Center
Gunma University
Mortality trends for leading causes of death in Japan

Incidence total: 749,767 pts (2008) (mail 37,787: female 311,980)
Death total: 357,305 pts (2011) (mail 213,190: female 144,115)

Death
1. Lung
2. Stomach
3. Colon/Rect.
4. Liver/Bile
5. Pancreas

Malignant Neoplasm
Cerebrovascular disease
Heart disease
Pneumonia

1981
Female Cancer Statistics in Japan

Mortality of cancers

1. Colon/Rect.
2. Lung
3. Stomach
4. Pancreas
5. Breast
6. Liver
7. Bile
8. Uterus

Incidences of cancers

1. Breast
2. Colon/Rect.
3. Stomach
4. Lung
5. Uterus
Difference in the treatment policy for cervical cancer

—Between Japan and USA—

<table>
<thead>
<tr>
<th>Stage</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>B</td>
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</tr>
</tbody>
</table>

Japan

Surgery  
Surgery  
Radiation

USA

Surgery  
Surgery  
Radiation

USA
Treatment Schedule of Combination of Ext. RT and Brachytherapy for stage 3 Cx

**HDR**

**USA**
- Whole pelvis field
- 6wk

**JPN**
- Whole pelvis field 20-30Gy
- Central shielding field 30-0Gy
- 5-7Gy/f
- 20-30Gy at point A

Brachytherapy
- Pelvis field RT
- C.S. field RT

- 30Gy
- 50Gy
- 70Gy
- 98Gy
Difference of composite EQD2 distribution between whole pelvis RT(WP) vs central shielding RT(CS)

EQD2 is expressed by biological equivalent dose by 2Gy/f and $\alpha/\beta=10$

WP 45Gy+ with Brachy 28Gy at point A

WP30Gy-CS 20Gy with Brachy 24Gy at point A
## Schedule of Brachytherapy

<table>
<thead>
<tr>
<th>Trials</th>
<th>Ext RT(Gy)</th>
<th>Dose rate</th>
<th>Dose</th>
<th>Point A Dose of Brachy</th>
<th>OTT(day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG9001</td>
<td>45</td>
<td>LDR</td>
<td>44</td>
<td>89</td>
<td>58</td>
</tr>
<tr>
<td>GOG85</td>
<td>40.8 - 51</td>
<td>LDR</td>
<td>30-40</td>
<td>81</td>
<td>63.7</td>
</tr>
<tr>
<td>GOG120</td>
<td>40.8 – 51</td>
<td>LDR</td>
<td>30-40</td>
<td>81</td>
<td>62.3</td>
</tr>
</tbody>
</table>

ABS schedule of HDR brachytherapy consists of Higher dose and long OTT than Japanese standard, but Japanese recommended dose have been confirmed by Japanese clinical experience.

Recommended dose by ABS was estimated from the dose of LDR

<table>
<thead>
<tr>
<th>ABS (III st)</th>
<th>45 – 50</th>
<th>LDR</th>
<th>40</th>
<th>85-90</th>
<th>&lt;56</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HDR</td>
<td>28 – 34.8</td>
<td>78 – 82</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Japan (III st)</th>
<th>50 (CS 10 – 30)</th>
<th>LDR</th>
<th>30 - 40</th>
<th>50 - 80</th>
<th>&lt;45</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HDR</td>
<td>15 – 20</td>
<td>35 – 60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(ABS recommendation, IJROBP 48:201-211,2000)
Cause-specific survival rates by stage (NIRS 1968~1986).

Follow up rate > 95%

Japanese protocol of radiation therapy for cervical cancer
Clinical results were reconfirmed by prospective multi-institutional study

Prospective multi-institutional study of definitive radiotherapy with high-dose-rate intracavitary brachytherapy in patients with nonbulky (<4-cm) stage I and II uterine cervical cancer (JAROG0401/JROSG04-2).


PDPF survival, OS, and DFS

Late complications (Grade ≥1)

(BED 62 Gy_{10} at point A).
The first evidence in Asia: FNCA CERVIX I-III

MULTI-INSTITUTIONAL PHASE II CLINICAL STUDY OF CONCURRENT CHEMORADIOThERAPY FOR LOCALLY ADVANCED CERVICAL CANCER IN EAST AND SOUTHEAST ASIA

Int J Radiat Oncol Biol Phys. 87, 1, 100-5 2013

Shingo Kato, M.D., * Tatsuya Ohno, M.D., † Kullathorn Thephamongkhol, M.D., ‡ Yaowalak Chansilpa, M.D., ‡ Yang Yuxing, M.D., § C. R. Beena Devi, M.D., ¶

FNCA: CERVIX-III (CCRT) N=120, 80%(2y)

FNCA: CERVIX-I (RT alone) N=210, 67%(2y)

GOG 120 (CCRT)

GOG 120 (RT+HU)
Image Guided H-D-R Brachytherapy for Cervical Cancer in Japan
# Imaging modalities in brachytherapy treatment planning

<table>
<thead>
<tr>
<th>Survey year</th>
<th>Pats.</th>
<th>Responses</th>
<th>2D plan</th>
<th>CT</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABS 1)</td>
<td>2007</td>
<td>256</td>
<td>55%</td>
<td>43%</td>
<td>55%</td>
</tr>
<tr>
<td>CANADA 2)</td>
<td>2009</td>
<td>58</td>
<td>62%</td>
<td>50%</td>
<td>45%</td>
</tr>
<tr>
<td>UK 3)</td>
<td>2008</td>
<td>45</td>
<td>96%</td>
<td>73%</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td>2011</td>
<td></td>
<td></td>
<td>26%</td>
<td>53%</td>
</tr>
<tr>
<td>JAPAN</td>
<td>2012</td>
<td>171</td>
<td>84%</td>
<td>84%</td>
<td>15%</td>
</tr>
</tbody>
</table>

3) Tan LT, et al. *Clinic Oncol* 2011

44% of institutions who responded are intending to initiate CT/MRI based 3D-IGBT in the next 3 years.
History of IGBT for cervical cancer in Japan
Clinical evaluation of MRI applied to brachytherapy for Cervical cancer


Decrease dose to fundus of uterus to sparing dose to OAR

HR-CTV

24Gy/4frs
Clinical evaluation of MRI applied to brachytherapy for Cervical cancer


MRI can evaluate radiation response after radiotherapy for cervical cancer.
Dose distribution analysis by DVH


Local control rate by absolute dose volume < 24Gy (6Gy/f x4)

48Gy + 30Gy = 78Gy (point A)

Local control

Recurrence
CT/MRI Based Planning System for Brachytherapy of Cervical Cancer

T. Nakano, Jap J Radiology 1998

Dose Distribution

Applicator for CT, MRI

Nakano-Chiyoda applicator

Composite Dose Distribution
MRI application
Bio-effect Distribution
DVH analysis

Bio-effect Distribution

Dose Distribution on MRI

DVH analysis
A set of non-metallic applicator for CT-MRI called Nakano-Chiyoda Applicator
In Room CT Based Planning System for Brachytherapy of Cervical Cancer (in 2000 NIRS)

Nakano T, Jap J Radiology 2000
In room CT-guided brachytherapy at Gunma Univ. (in 2003)

There are 7 institutions equipped with in-room CT for Brachytherapy: NIRS, Gunma Univ., Tsukuba Univ., Saitama Int.Nat. Med. Center, NCC, Nagoya Univ., Ganken Hp.
History of IGBT for cervical cancer in Japan

1987 Clinical evaluation of MRI applied to brachytherapy for Cervical cancer


1998 Brachytheapry treatment planning system based on CT image and MRI.
_Nakano T, Jap J Radiology 1998_

2000 Introduction of in room CT for IGBT for cervical caner in NIRS.
_Nakano T, Jap J Radiology 2000_

2003 Introduction of in-room CT for IGBT for cervical caner in Gunma Univ..

2005 GEC-ESTRO Recommendation 1

2006 GEC-ESTRO Recommendation 2
(Pötter R et al., Radiother Oncol 78: 67–77, 2006)

2007 Hybrid IGBT for cervical cancer at Gunma Univ.

2009 GEC-ESTRO Guideline of Image Guided Brachythehrapy
_Dimopoulos JC et al., Radiotherapy and Oncology, Vol. 93, pp. 311-5, 2009_
Criticism to Japanese radiation oncologist

I have developed the IGBT at NIRS during 1990s in Japan and it was too early to be adopted to Japanese brachytherapy circumstances.

The leaders of brachytherapy for cervical cancer at that time in Japan did not try to introduce and disseminate the IGBT in Japan until 2010 and keep 2D planning because of rather good clinical results obtained by conventional 2D planning due to time consuming modality and heavy load of IGBT for busy RO in Japan.

Therefore we could not promote and establish standard protocol of IGBT in Japan.

Now it is time to promote and establish standard protocol of IGBT in Japan.
3D IGBT for Cervical cancer
Image-based brachytherapy / Image-guided brachytherapy

\( D_{90} \) of HR-CTV
Minimum dose (Gy) of 90% HR-CTV

\( D_{2cc} (D_{0.1cc}, D_{1cc}) \)
Mini dose (Gy) of highest dose area of 2cc at OAR.

Microscopic tumor area with GTV and Cervix by Exam and MRI

(Pötter R et al., Radiotherapy and Oncology 78;67-77, 2006.)
Cumulative EQD2 distributions using DIR (WP 30 Gy + CS 20 Gy + ICBT > 24 Gy/4Fr to HR-CTV D90)
Difference in Modality between the two University
Gunma Univ. and Vienna Univ.

1. Dosage
   Gunma Univ: 30 Gy + 6 Gy x 4 (EQD$_2$ = 62.0)
   Vienna Univ.: 45 Gy + 7 Gy x 4 (EQD$_2$ = 83.9), x1.35?

2. Time of Brachy.
   → different dose to tumore and OARs
2. TPS based on CT and MRI (larger volume by CT?)
3. Overall treatment time (short in Japanese)

Volume of HR-CTV

Vienna Univ.

ERT45Gy, 5w

Gunma Univ.

ERT30Gy, 3.5w

Central Shielding, 2w

8 weeks

6 weeks
Correlation of rectal dose with late rectal complications

The composite dose to the rectum by whole pelvis irradiation and high-dose-rate brachytherapy, is calculated by use of EQ dose by 2Gy/f with α/β ratio of 3. rectal dose estimated at anterior wall of rectum identified with both CT images and ICRU.

Dose-Volume Parameters and rectal complications (1)

D0.1-2cc of the rectum significantly correlated with endoscopic findings (VRS$\geq3$: confluent telangiectasia - ulcer) and clinical symptoms (LENT/SOMA $>2$).

CT-based 3D Dose-Volume Parameter of the Rectum and Late Rectal Complication in Patients with Cervical Cancer Treated with High-Dose-Rate Intracavitary Brachytherapy

Shingo KATO, TRAN Dang Ngoc Linh, Tatsuya OHNO, Takashi NAKANO, et al.  

**Table 1.** Comparison of the values of dosimetric parameters between patients with and without late rectal complications (all Grades).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LRC (−) n = 64</th>
<th>LRC (+) n = 20</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DICRU</td>
<td>73.9 (11.5–125.8)</td>
<td>83.4 (43.5–127.8)</td>
<td>p = 0.1</td>
</tr>
<tr>
<td>D0.1cc</td>
<td>77.3 (15.0–157.2)</td>
<td>111.4 (54.8–156.1)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>D1cc</td>
<td>61.7 (13.2–115.8)</td>
<td>85.4 (51.0–136.9)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>D2cc</td>
<td>53.9 (12.1– 93.0)</td>
<td>72.0 (44.1– 99.3)</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

Abbreviations: LRC, late rectal complication; EQD2, biologically equivalent dose in 2-Gy fractions; ICRU, International Commission on Radiation Units and Measurements.
Highly Precise Image-Guided Brachytherapy

CT image guided interstitial Brachytherapy

Intracavitary Brachy.  Interstitial Brachy.

Tumor is larger than dose area of radical intent

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR-CTV volume</td>
<td>103</td>
<td>(33–174)</td>
</tr>
<tr>
<td>D100 (Gy)</td>
<td>3.3</td>
<td>(2.3–4.0)</td>
</tr>
<tr>
<td><strong>D90 (Gy)</strong></td>
<td>5.7</td>
<td>(4.7–6.4)</td>
</tr>
<tr>
<td>V100 (%)</td>
<td>87</td>
<td>(72–94)</td>
</tr>
<tr>
<td>D2cc of the bladder (Gy)</td>
<td>4.9</td>
<td>(4.1–5.7)</td>
</tr>
<tr>
<td>D2cc of the rectum (Gy)</td>
<td>4.7</td>
<td>(2.7–7.4)</td>
</tr>
</tbody>
</table>

3y Pelvic control rate 71% (n=15)

Adjustment of Dose Distribution of Brachytherapy by Additional Needle (Hybrid Brachytherapy)

Ultrasound images are very useful for any application in order for safe practice.
Adjustment of Dose Distribution by Additional Needle (Hybrid Brachytherapy)

Comparison of DVHs by Brachytherapy Modalities

- Intracavitary Brachy.
- Hybrid Brachy.
- Interstitial Brachy.

Better tumor coverage with sparing OAR
Hybrid brachytherapy
Cervical cancer (FIGO IIb, Sq, RT)

Before treatment

46 Mo. NER

Hybrid Brachytherapy

13 pts of 22 pts were followed for over 2 years in 2012

1) Toita et al. Gynecol Oncol 2012

<table>
<thead>
<tr>
<th>Pt Number</th>
<th>JGOG1066</th>
<th>CCRT</th>
<th>Gunma Univ.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
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<td>3</td>
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<td>4</td>
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<td>13</td>
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</table>

<table>
<thead>
<tr>
<th>No. pts</th>
<th>Tumor $\phi$</th>
<th>2y pelvic control</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>JGOG1066</td>
<td>32</td>
<td>5—7cm</td>
<td>72%</td>
</tr>
<tr>
<td>CCRT</td>
<td>13</td>
<td>7cm $&lt;$</td>
<td>54%</td>
</tr>
<tr>
<td>Gunma Univ.</td>
<td>13</td>
<td>6.2cm median (4.7—9.4cm)</td>
<td>84%</td>
</tr>
</tbody>
</table>

Graph:
- Pelvic control rate: 84%
- Overall survival

Initial serum SCC:
- JGOG1066: 2.6, 46.1, 63.1
- CCRT: 2.5, 2.0, 3.2, 7.3, 1.7, 12.2, 10.7, 51.3
- Gunma Univ.: 6.8
Dose distribution of various RT modalities

Inhomogeneity of Dose in GTV

AP-PA Ext. RT
IMRT

Particle RT

Intracavitary Brachy.

Interstitial Brachy.

Hybrid Brachy.

100%
Inhomogeneity of Dose in GTV

- AP-PA Ext. RT
- Particle RT
- Interstitial Brachy
- Intracavitary Brachy
- Hybrid Brachy

Relative dose volume

- 100% dose
- x 1.2
- x 3
- dose
Summary

- Doses of Japanese brachytherapy system are smaller than European and USA standard, because central shielding pelvis fields is applied for external pelvis irradiation and over all treatment time is shorter.

- Guideline of radiotherapy for cervical cancer was established officially in 1984 by Japan Society of Obstet. Gynecol.

- Image guided brachytherapy by use of CT and MRI have been introduced in Japan in early 1990s and in room CT in early 2000s, but it has not been widely utilized and not been standardized in Japan.

- IGBT technic for optimization of dose distribution of brachytherapy by additional needle (Hybrid brachytherapy) was developed at Gunma university to improve local control for bulky cervical cancers.

- IGBT is expected to improve local control for bulky cervical cancers, but to be confirmed by accumulation of substantial long term qualified clinical data.
Professor E. Tazaki

Professor T. Arai
Thank you very much for your attention!