Image-guided brachytherapy (IGBT) combined with whole pelvic intensity-modulated radiotherapy (WP-IMRT) for locally advanced cervical cancer: a prospective study from Chiang Mai University Hospital, Thailand

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Abstract

Purpose: A report of preliminary results and toxicity profiles using image-guided brachytherapy (IGBT) combined with whole pelvic intensity-modulated radiation therapy (WP-IMRT) for locally advanced cervical cancer.

Material and methods: Fifteen patients with locally advanced cervical cancer were enrolled into the study. WP-IMRT was used to treat the Clinical Target Volume (CTV) with a dose of 45 Gy in 25 fractions. Concurrent cisplatin (40 mg/m²) was prescribed during radiotherapy (RT) on weekly basis. IGBT using computed tomography was performed at the dose of 7 Gy × 4 fractions to the High-Risk Clinical Target Volume (HR-CTV).

Results: The mean cumulative doses – in terms of equivalent dose of 2 Gy (EQD2) – of IGBT plus WP-IMRT to HR-CTV, bladder, rectum, and sigmoid colon were 88.3, 85.0, 68.2 and 73.6 Gy, respectively. In comparison with standard (point A prescription) dose-volume histograms, volume-based image-guided brachytherapy improved the cumulative doses for bladder of 67%, rectum of 47% and sigmoid of 46%. At the median follow-up time of 14 months, the local control, metastasis-free survival and overall survival rates were 93%, 100% and 93%, respectively. No grade 3-4 acute and late toxicities were observed.

Conclusion: The combination of image-guided brachytherapy and intensity-modulated radiotherapy improved the dose distribution to tumor volumes and avoided overdose in OARs which could be converted in excellent local control and toxicity profiles.

Key words: brachytherapy, cervical cancer, IGBT, IMRT.
EBRT, intensity-modulated radiation therapy (IMRT) is increasingly being used to treat cervical cancer and has the potential to improve the therapeutic ratio because of its ability to escalate the dose to cancer targets while sparing adjacent healthy tissue [5]. A few studies for IMRT in gynecological cancer showed that IMRT reduced the dose to OAR—bowels, bladder and rectum [6,7]. Respecting the principles of inverse-square law, brachytherapy delivers very high doses to the primary tumor (close to radioisotope) while it deposits substantially less dose to the surrounding OAR (bladder, rectum, and sigmoid). Although the use of conventional X-ray based planning can get good outcomes and acceptable toxicities, many limitations are associated with this process. With the emerging of Groupe Européen de Curithérapie – European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) recommendations, the developed volume-based concept seems to be associated with an improvement of brachytherapy for the treatment of cervical cancer [8,9]. Many studies support the use of image-guided brachytherapy (IGBT) to improve therapeutic ratios in cervical cancer [10-12].

With the developments of radiotherapy techniques such as IMRT and IGBT, the combinations of these techniques of irradiation need to be studied. Therefore, we performed this groundwork study to report preliminary results and toxicity profiles of combined IMRT and IGBT for determining optimal treatment of cervical cancer and defining a new workflow in our department in terms of refining and improving the process quality in modern radiotherapy.

Material and methods

The study took place from January 2011 to January 2012. Seventeen patients with cervical cancer were included and treated in the Division of Therapeutic Radiology and Oncology, Faculty of Medicine, Chiang Mai University. All patients were classified IIB-IIIB by FIGO clinical staging, were between 18–70 years old and had good performance status. Patients with severe co-morbidity, emergency conditions (e.g. bleeding) that could not permit delays in treatment, pregnancy, history of previous irradiation or allergy were excluded from the study. Consent forms were signed by each patient prior to enrollment. Two patients were excluded from the study during treatment because of too large tumor extension for performing intracavitary brachytherapy, as a result fifteen patients were actually evaluated. The patient characteristic data appear in Table 1.

Whole pelvic IMRT (WP-IMRT)

All patients received EBRT of 45 Gy using IMRT. At the beginning, a CT simulation was performed. Vac-Loc was used to immobilize patients positioning. To prepare the bladder, patients were advised to urinate twenty minutes before scanning and they drank 200 ml of water after voiding. Twenty minutes later, patients were set up in CT. This protocol was used during irradiation to maintain bladder volume. For rectal preparation, a laxative was administered in case of rectal dilatation. The pelvic region from the L1-2 interspace to the whole vagina was scanned without intravenous contrast to obtain appropriate images with the patients in supine treatment position and legs relaxed on the table. The slice thickness of CT scans was 5 mm without an inter-slice gap. After imaging process was completed, image data were sent to the Contouring (Oncentra Masterplan®, Nuclertron, an Elekta company, Elekta AB, Stockholm, Sweden) and Treatment Planning (KonRad treatment planning software®, Siemens, Concord, CA, USA). For the identification of Clinical Target Volume (CTV), the RTOG/JCOG recommendations were used in combination as a guide for contouring [13-16]. The Clinical Target Volume (CTV) was composed of cervix, uterus, adnexae, the upper half of vagina, and pelvic lymph nodes (common iliac lymph nodes [LNs], external iliac LNs, internal iliac LNs, obturator LNs and presacral LNs). Planning Target Volume (PTV) was defined by CTV plus 0.7-1.5 cm margin. Bladder, rectum, sigmoid colon, bowels and head of femurs were contoured as OARs. For CTV, the dose of 1.8 Gy per fraction, five fractions per week was prescribed to the total dose of 45 Gy. Figures 1A-B show contours and dose distributions for WP-IMRT. The priorities were prescribed as following: CTV, bladder, rectum, sigmoid, bowel, and head of femur. The D90 (dose at 90% of volume) of CTV was calculated. For OARs, the doses at D2% of bladder, rectum and sigmoid colon were recorded for dose evaluation. During irradiation, patients were advised to prepare bladder and rectum such as with CT simulations. Electronic portal imaging devices (EPID) was used weekly to evaluate and correct for actual position. The CTV and OARs doses were calculated into equivalent dose in 2 Gy-fractions (EQD2) using the linear-quadratic model and assuming $\alpha/\beta$ ratio = 10 for tumor and $\alpha/\beta$ ratio = 3 for OARs [17].

Concurrent chemoradiation

Concurrent chemoradiation with weekly cisplatin 40 mg/m² for a maximum of five cycles was given to patients with an indication of combined radio-chemotherapy with sufficient kidney and bone marrow function. The dose of chemotherapy was modified according to a weekly assessment of creatinine clearance prior to each applied dose. Chemotherapy was interrupted when creatinine clearance was less than 40 ml/min and considered to be stopped when creatinine clearance was less than 30 ml/min.

### Table 1. Characteristic data of patients in the study

| Parameters              | Data (mean; range) |
|-------------------------|--------------------|
| Age                     | 53 years (range: 47-61 years) |
| Pathology:              |                    |
| SCCA                    | 13                 |
| ACA                     | 2                  |
| FIGO stages:            |                    |
| IIB                     | 12                 |
| IIIB                    | 3                  |
| Total treatment time    | 54 days (range: 42-74 days) |

SCCA – squamous cell carcinoma, ACA – adenocarcinoma, FIGO – the International Federation of Gynecology and Obstetrics
Image-guided brachytherapy (IGBT)

Four fractions of high-dose rate intracavitary brachytherapy with iodium-192 radioisotope were designed for all patients. First brachytherapy application was assigned to be performed after the 4th week of EBRT. Intracavitary applicators were used. A Foley’s catheter was inserted in the bladder and inflated with 7 cc of diluted contrast media. A normal saline solution (50 cc) plus 10 cc of contrast media was added into the bladder to identify bladder volume before CT imaging. The vagina was packed with gauze to increase the distance between the radiation source and the rectum/bladder. EBRT was interrupted for each day of HDR brachytherapy insertion. After application, a pelvic CT scan was performed from the iliac crest to the ischial tuberosity without intravenous contrast to obtain appropriate images with the patients in a supine treatment position and legs relaxed on the table. The slice thickness of CT scans was 5 mm without an inter-slice gap. After the imaging was performed, images were checked by the radiation oncologist and then transported to the planning system. For the planning system, we used PLATO software (software BPS version 3.3.2®, Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden) for the contouring and planning process. Patients were then transferred to the brachytherapy treatment room and adjusted to the same position as in the imaging devices.

High-risk clinical target volume (HR-CTV), intermediate-risk clinical target volume (IR-CTV) and OARs (bladder, rectum and sigmoid colon) were contoured according to the CT-standardized contour guidelines of Viswanathan et al. [18]. Delineation of HR-CTV was performed based on CT information at the time of brachytherapy supported by further available clinical findings. HR-CTV was identified by the volume carrying a high probability of tumor: the whole cervix and the presumed extra-cervical tumor extension at the time of brachytherapy. OARs were defined as bladder, rectum and sigmoid colon. The rectum was contoured from the anal-rectal to the recto-sigmoid junction. Delineation of the sigmoid colon started at the recto-sigmoid junction and ended 2 cm above the uterus. Bladder was contoured as an entire organ. Figures 2A-B show contours and dose distributions for IGBT.

The prescribed dose was at least 7 Gy × 4 fractions to HR-CTV (volume-based plan) for all patients. Dose-volume histograms (DVHs) to HR-CTV and OARs were evaluated. The prescription to point A was also prescribed at 7 Gy to evaluate DVHs as standard “point-based” plan. For HR-CTV, the D90 (minimum dose covering 90% of target volume) of HR-CTV in all patients was recorded. For OARs, the D2cc (representing the minimum doses calculated at the most irradiated 2 cc volumes) of bladder, rectum, and sigmoid colon were recorded. The HR-CTV and OARs total doses (WP-IMRT and IGBT) were calculated into equivalent doses in 2 Gy-fractions (EQD2) using the linear-quadratic model and assuming α/β ratio = 10 for tumor and α/β = 3 for OAR [17]. The EQD2 of WP-IMRT and IGBT were added to evaluate the volume-based plan with regards to the DVH constraints corresponding to a prescribed dose of at least 80 Gy10 for tumor (D98% of WP-IMRT plus D90% of IGBT). For the OAR, total dose (D2% of WP-IMRT plus D2cc of IGBT)
constraints maintained ≤ 75 Gyα/β for rectum/sigmoid and ≤ 90 Gyα/β for the bladder, respectively. For standard plans, the EQD summation of WP-IMRT of HR-CTV (D98% of WP-IMRT plus D90% of HR-CTV) and OARs (D2% of WP-IMRT plus D2cc of OARs) were calculated and compared with volume-based plans.

**Evaluation**

During treatment, patients visited the physician to evaluate the toxicities according to the National Cancer Institute, USA; Common Terminology Criteria of Adverse Event (CTCAE) version 3.0. After the treatment was completed, patients were appointed for a vaginal examination (PV exam) in a follow-up program. The vaginal examination was performed to evaluate the disease status according to the World Health Organization (WHO) criteria. Late toxicities were evaluated according to the Radiation Therapy Oncology Group/ European Organization of Research and Treatment of Cancer (RTOG/EORTC) late toxicity criteria.

**Statistical analysis**

All statistical analyses were evaluated by SPSS version 17.0. Descriptive statistics were calculated and reported at the terms of mean and range. The comparison between doses of volume-based plans versus standard (point A) plans in terms of GEC-ESTRO recommendations was performed by paired t-test (two-tailed test) to defined statistical significance level of \( p < 0.05 \).

**Results**

All patients completed the treatment process. At median follow-up time of 14 months (range 6-18 months), one patient developed a recurrence after six months of treatment, confirmed by biopsy. One patient died from non-cancer cause six months after starting the treatment. Thus, the local control, metastasis-free survival and overall survival rates were 93%, 100% and 93%, respectively. The volume-based IGBT planning improved dose distribution for HR-CTV and OARs in comparison with standard plans. For WP-IMRT the mean dose to 98% of CTV, 2% of bladder, 2% of rectum and 2% of sigmoid colon were 42.4 ± 1.3 Gy, 46.7 ± 3.2 Gy, 46.4 ± 4 Gy and 48.9 ± 3.3 Gy, respectively. The mean volume of HR-CTV was 22.03 cc (range; 11.5-40.2 cc). Three patients (20%) had at 1st application a HR-CTV volume more than 30 cc. The mean cumulative EQD2 doses to HR-CTV, bladder, rectum, and sigmoid for standard plans were 109.81, 113.86, 79.84 and 90.85 Gy, respectively. The mean cumulative EQD2 doses of volume-based plans were 88.3, 85, 68.15 and 73.64, respectively. This data is detailed in Table 2. For OARs, the volume-based planning of IGBT in comparison to standard plans could also reduce the cumulative overdose from 80% of patients (12/15) to 13% of patients (2/15) for bladder (> 95 Gy EQD2), from 53% of patients (8/15) to 6% of patients (1/15) for rectum (> 75 Gy EQD2), and from 86% (13/15) to 40% (6/15) for sigmoid colon (> 75 Gy EQD2). In terms of acute toxicity, nine patients (60%) developed Grade 1-2 for proctitis and eight patients (53%) had grade 1-2 cystitis. Complete acute toxicity data is presented in Table 3. In one-year follow-up, no patient developed late toxicity except one patient with an event of Grade 1 vaginal stenosis.

**Discussion**

The improvement of the technology in radiotherapy has helped us to enhance the radio-therapeutic ratio. In terms of EBRT, the development of IMRT was important to be investigated. WP-IMRT was studied in combination to conventional brachytherapy in clinical aspects. The study by Portelance et al. showed that the fraction of rectal overdose with WP-IMRT was lower than conventional (2 or 4 fields) technique \( (p < 0.001) \) [19]. In the study by Hasselle et al. 101 patients were enrolled and 81 patients were treated with IMRT, followed by conventionally planned intracavitary brachytherapy. Of these patients, 63 had stage I-IIA disease and 48 had stage IIB-IVA disease. The median follow-up time was 27 months. The 3-year overall survival rate and the disease-free survival rate were 78% (95% confidence interval [CI]: 68-88%) and 69% (95% CI: 59-81%), respectively. The 3-year pelvic failure rate and the distant failure rate were 14% (95% CI: 6-22%) and 17% (95% CI: 8-25%), respectively. Estimates of acute and late grade 3 toxicity or higher were 2% (95% CI: 0-7%) and 7% (95% CI: 2-13%), respectively [7]. Moreover, Chen et al. reported a retrospective study using IMRT with chemotherapy in 109 patients with stage IB2-IVA cervical cancer. The dose of 45-54 Gy with IMRT technique and 20-33.5 Gy by brachytherapy at point A were used. At the median follow-up time of 32.5 months, the 3-year overall survival, local failure-free survival and disease-free survival rates were 78.2%, 78.1% and 67.6%, respectively. Three patients developed grade 3 or greater acute GI toxicity and 26 patients developed grade 3 or greater hematological toxicity. Five patients developed late GI toxicity except one patient with an event of Grade 1 vaginal stenosis.

**Table 2.** Cumulative dose in EQD2 of point-based plan versus volume-based plan

| Parameters | Point-based plan: Gy (mean ± SD) | Optimized plan: Gy (mean ± SD) | P-value (2-tailed) |
|------------|----------------------------------|--------------------------------|--------------------|
| HR-CTV     | 109.8 ± 16.3                     | 88.3 ± 3.8                    | < 0.001            |
| Bladder    | 113.9 ± 28.8                     | 85.0 ± 9.3                    | < 0.001            |
| Rectum     | 79.8 ± 16.2                      | 68.2 ± 6.5                    | 0.001              |
| Sigmoid    | 90.8 ± 15                        | 73.6 ± 6.3                    | < 0.001            |

**Table 3.** Acute toxicities of cervical cancer of combination of WP-IMRT plus IGBT

| Parameters                      | Numbers of patients |
|--------------------------------|---------------------|
| Skin G1-2                       | 1                   |
| Skin G3-4                       | 0                   |
| Gastrointestinal toxicity (proctitis) G1-2 | 9                   |
| Gastrointestinal toxicity (proctitis) G3-4 | 0                   |
| Genitourinary toxicity (cystitis) G1-2 | 8                   |
| Genitourinary toxicity (cystitis) G3-4 | 0                   |
Table 4. The published studies compared the conventional plan versus optimized plan in many methods

| Studies                  | N   | Methods                           | Results                                      |
|--------------------------|-----|-----------------------------------|----------------------------------------------|
| De Brabandere et al. [21]| 16  | DVHs of X-ray based plan versus optimization | Overdose of the D_{2cc} for bladder = 10/16 and rectum = 7/16. After optimization, no overdose was found. |
| Tanderup et al. [22]     | 70  | Point doses were compared to three-dimensional dose parameters | In HR-CTV < 31 cc, the coverage by standard plan = 94%, OARs exceeded = 72%. OARs overdose reduced to 6% in optimization. In HR-CTV > 31 cc, the coverage by standard plan = 25% and the coverage improved to 72% after optimization. With optimization, the coverage improved to 72%. |
| Zwahlen et al. [23]      | 20  | Optimized plan versus conventional plan | Optimized plan improved the coverage of HR-CTV from 70% to 75% and the dose to OARs could be reduced 12-32%. |

Table 5. The published studies of clinical results of image-guided brachytherapy

| Studies                  | N   | Results                          | Toxicity                                      |
|--------------------------|-----|----------------------------------|-----------------------------------------------|
| Pötter et al. [11]       | 156 | 3-yr LC rate 95%, 3-yr CSS rate 74% and 3-yr OS rate 68% | G2-4 bladder 3 events, G3-4 rectum 5 events, G3-4 sigmoid 0 events and G3-4 vagina 2 events |
| Tan et al. [12]          | 28  | 3-yr CSS rate 81% and pelvic control rate 96% | Serious late morbidity rate 14% |
| Haie-Meder et al. [24]   | 84  | 4-year OS rate 57% and 4-year DFS rate 52% | Four patients had grade 3 complications |
| Charra-Brunaud et al. [25]| 117 | Twenty-four months local relapse-free survival rate 78.5% | Grade 3-4 complications 2.6% |
| Beriwal et al. [26]      | 44  | The 2 year LC rate 88%, 2-year CSS rate 85% and 2-year OS rate 86% | NA |

LC – local control, CSS – cancer-specific survival, OS – overall survival, DFS – disease-free survival, yr – years

dev eloped grade 3 or greater chronic GI toxicity and seven patients developed grade 3 or greater GU toxicity. Although these two clinical trials used advanced technologies (IMRT) for the external beam treatment of the whole pelvis in cervical cancer with promising results, conventional brachytherapy only was used in these studies to boost the high-risk clinical target volume. [20]. In the era of IGBT, many studies reported the results of conventional versus IGBT planning approaching different technical solutions. All reports showed in conventional planning, causing inadequate dose to target volumes or overdose to OARs. With optimization, the dose to HR-CTV and OARs were improved. All studies are shown in Table 4 [21-23]. Our approach was to combine the benefits of high-technology EBRT and IGBT. Besides data concerning, dosimetry comparison between conventional and image-guided and volume-optimized brachytherapy planning, also short and long-term clinical outcomes were reported. Many studies reported the promising results of various schedules of IGBT in tumor control and late toxicities (Table 5) [10-12, 24-26].

In our experience, volume-based IGBT combined with WP-IMRT improved the dose distributions in HR-CTV and OARs compared with standard planning [27,28]. The mean cumulative EQD2 doses to HR-CTV could be maintained higher than 80 Gy in EQD2. For OARs, the volume-based planning of IGBT in comparison to standard plans could also reduce the cumulative dose for bladder (EQD2 113.9 vs. 85 Gy, p < 0.001), for rectum (EQD2 79.8 vs. 68.2 Gy, p = 0.001), and for sigmoid colon (EQD2 90.8 vs. 73.6 Gy, p < 0.001). These results demonstrate the significant potential of volume-based IGBT planning in reducing treatment related acute and late morbidity, while ensuring a sufficient curative dose to HR-CTV. The mean HR-CTV in the present study was 22 cc and thus the benefit of image-guided brachytherapy was mainly to reduce the exceeding dose to the OARs which is in concordance with the literature [22]. When considering a minimum cumulative dose of HR-CTV, all patients in the present study reached a cumulative EQD2 > 80 Gy which represented the highest constraint priority. In the patient who developed a local recurrence, the cumulative EQD2 to the HR-CTV was high enough with 89.4 Gy. In conclusion, our first intermediate-term results are very promising with a median follow-up time of 14 months, and disease-free survival, metastasis-free survival and overall survival rates of 93%, 100% and 93%, respectively. No serious acute toxicity could be observed. The common toxicities were grade 1-2 proctitis (9 patients) and grade 1-2 cystitis (8 patients). Due to concurrent chemo-radiation, 5 patients (33%) and 4 patients (26%) had grade 1-2 leucopenia and grade 1-2 anemia, respectively. No late toxicity was registered during the follow-up period except one patient with a grade 1 vaginal stenosis.

However, high-precision methods are more time consuming than conventional techniques which may cause more workload in the process of logistics, planning and execution of the treatment. Therefore, the summation of WP-IMRT and image-guided brachytherapy remains controversial. Further follow-up is necessary in order to evaluate the potential benefits of these sophisticated techniques in terms of long-term outcomes. The equivalent dose of 2 Gy (EQD2) was used in our study to calculate the dose to tumors and OARs. In this context, we assumed the summation of D_{98%} of WP-IMRT (CTV) and D_{95%} of IGBT (HR-CTV) for tumor dose and the D_{2cc} of WP-IMRT plus D_{2cc} of IGBT.
for OARs doses to be significant in the evaluation of treatment quality. Prospectively, we intend to test these dosimetry measures in long-term follow-up for significance and prediction potential especially according the endpoints local control and late toxicity.

Conclusion
The combination of IGBT and WP-IMRT helped to improve significantly the target coverage, while it maintained high curative doses for HR-CTV and avoiding overdose in OARs.

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