Preliminary Results of MRI-guided Brachytherapy in Cervical Carcinoma: The Chiangmai University Experience

Ekkasit THARAVICHITKUL1*, Chate SIVASOMBOON2, Somsak WANWILAIRAT1, Vicharn LORVIDHAYA1, Vimol SUKTHOMYA1, Somvilai CHAKRABHANDU1, Sanchai LOOKKAEW1, Imjai CHITAPANARUX1 and Razvan GALALAE3

Advanced cervical cancer/Intracavitary/interstitial brachytherapy/Conformal MRI-based planning.

This study was performed to evaluate the feasibility of magnetic resonance imaging (MRI) in the treatment planning of image-guided brachytherapy for cervical carcinoma. Seventeen consecutive patients with locally advanced cervical cancer were enrolled in the study. Fifteen patients could be evaluated. When comparing the tumor at diagnosis (GTV-Dx) and the tumor at the first brachytherapy (GTV-BT), 11 of 15 patients showed a tumor regression of more than 80% while only four patients had less than 80% tumor regression. The mean D90 of HR-CTV and the calculated D2cc of the bladder, rectum, and sigmoid were 99.2 ± 11 Gy, 87.7 ± 5.7 Gy, 68.4 ± 5.4 Gy and 70.3 ± 6.8 Gy, respectively. No grade 3–4 acute toxicity was observed. The MRI can be a valuable tool for evaluating tumor response after external beam radiotherapy (EBRT) and is very helpful for prognosis prediction by residual GTV evaluation. Furthermore, MRI-guided brachytherapy allowed us to optimize the dose for both the target volumes and the OARs.

INTRODUCTION

Carcinoma of the cervix is one of the most frequent cancer entities in women in Asia. The treatment options for cervical cancer are composed of surgery, radiotherapy and chemotherapy according to the stage and performance status of each patient. Radiotherapy plays many roles in early and advanced stage disease. For early disease, which is medically inoperable, radiotherapy constitutes the major treatment procedure, while the treatment of locally advanced disease is based on a combination of radiotherapy and chemotherapy. With concurrent chemoradiation, treatment results have shown improvement in locally advanced cervical cancer.1–3) Thus, the combination treatment of external beam radiotherapy (EBRT) and brachytherapy (BT) has become the standard treatment in advanced disease. EBRT (45–60 Gy) aims to control the microscopic and macroscopic disease in the primary tumor and lymph nodes in the pelvic area and BT is used to boost the dose to the local lesion up to 70–90 Gy according to the stage. Respecting the principles of inverse-square law, brachytherapy delivers very high doses to the primary tumor (close to radioisotope) while it deposits a substantially smaller dose to the surrounding organs at risk (bladder, rectum, and sigmoid). The most common usage of brachytherapy techniques for carcinoma of cervix uteri is intracavitary brachytherapy. It is composed of the tandem applications of intrauterine plus vaginal colpostats or rings at the vaginal fornix. The dose prescription to point A by the Manchester concept and the International Commission of Radiological Unit (ICRU) points of bladder and rectal points is generally used as the standard treatment based on x-ray imaging.4) Although the utilization of conventional x-ray based planning can result in good outcomes and acceptable toxicities, many limitations are associated with conventional planning. However, by the use of the new imaging modalities e.g. computed tomography (CT) or magnetic resonance imaging (MRI) target volumes can be defined with greater accuracy. Furthermore, point A does not represent the true target volume in patients with complex tumor form/volume (target volumes are smaller or larger than defined by point A). Secondly, the use of ICRU points in organs at risk (bladder, rectum, sigmoid) in the context of conventional planning cannot avoid the deposition of relatively high doses to the OARs. Thus, with the increasing availability of modern imaging, newcomers for radiotherapy planning revealed
clear evidence and proved these imaging tools to be extremely useful for the treatment of complex shaped cervical cancers with an excellent achievable quality of image-based, 3D volume-based brachytherapy. With the emerging of Groupe Européen de Curiethérapie – European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) recommendations in 2005–2006, the MRI-guided brachytherapy seemed to be the best treatment guidance.5,6)

The MRI provides more accurate target differentiation and normal tissue segmentation compared to other planning/treatment modalities. The study of Viswanathan et al. showed that the MRI was superior to the CT for target localization and treatment optimization7) due to its better soft tissue contrast. Thus, we performed this preliminary study to evaluate the efficacy and feasibility of MRI-guided brachytherapy in cervical carcinoma determining and defining new workflows in our department in terms of refinement and improvement of process quality in modern radiotherapy.

MATERIALS AND METHODS

From February 2009 to March 2011, seventeen patients with carcinoma of cervix uteri were included in this study. All of these patients were classified as IIB-IIIB by FIGO clinical staging, were 18–70 years old and had a Karnofsky performance status of more than 70. Patients with a severe co-morbidity, an emergency condition (e.g. bleeding that could not allow for treatment initiation delay due to complex planning process), pregnancy, previous irradiation or history of allergies were excluded from the study. Informed consents were signed by all patients before enrollment.

Radiotherapy techniques

All patients received whole pelvis irradiation to the total dose of 45 Gy in 25 fractions. Parametrial boost to 50.4 Gy was considered individually for each patient. The patients received whole pelvic 3D conformal EBRT using a four-field box technique with individual blocks based on CT-assisted 3D treatment planning. The clinical target volume (CTV) was defined as an area of potential microscopic disease and included the gross tumor volume, whole cervix, entire uterus, parametrical tissue, and two cm of the upper vagina, common iliac nodes, external iliac nodes, internal iliac nodes, obturator nodes, and pre-sacral lymph nodes. The lymph node groups were contoured according to the recommendations of Taylor et al.8)

Concomitant chemotherapy with weekly cisplatin 40 mg/m² for a maximum of five courses was given to patients with indication of combined chemoradiotherapy 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.

Four fractions of intracavitary brachytherapy were designed for all patients. The first brachytherapy application was assigned to be performed after the fourth week of EBRT. A dose of 7 Gy per fraction (in total four fractions) to point A (ICRU 38) was applied. CT/MR applicators (Fletcher, Tandem/ring, and Utrecht applicators) were used. A Foley’s catheter was placed in the bladder and inflated with 7 cc of diluted contrast media. A normal saline solution (50 cc) plus 10 cc of contrast media were added into the bladder to identify the bladder volume on planning imaging. The vagina was packed with gauze to increase the distance between the radiation source, and the rectum and bladder. The EBRT was interrupted for each day of HDR brachytherapy insertion. After application, all patients were transferred to MRI (1st application and CT for others), and the pelvic region from the iliac crest to the ischial tuberosity was scanned without intravenous contrast to obtain appropriate images with the patients in a supine treatment position with their legs relaxed on the table. The slice thickness of MRI and CT scans was 5 mm without an inter-slice gap. After the imaging was performed, the position of the applicators was checked and imaging data was collected by the radiation oncologist before being transferred to the planning system. Patients were then transferred to the brachytherapy treatment room and adjusted to the same position as in the imaging devices. The Magnetic Resonance Imaging (MRI) was used for the first brachytherapy planning (in addition to CT) and initially at diagnosis, as well as three months after treatment for the first evaluation.

For MRI, GEC-ESTRO definitions were used to identify target volumes e.g. Gross Tumor Volume (GTV) or High-Risk Clinical Target Volume (HR-CTV), and Organs at risk (OARs).9) Dose-volume histograms were calculated to consider the adequate dose to HR-CTV and limitations of OARs. In CT imaging, all HR-CTV and OARs were contoured according to the CT-standardized Contour Guidelines of Viswanathan et al.7) MRI images from the first application were used to guide contouring in CT images of other applications.

The D90 (minimum dose covering 90% volumes) of the HR-CTV and D2cc (representing the maximum doses calculated at the most irradiated 2 cc volumes) of OARs were recorded according to GEC-ESTRO recommendations. The prescribed dose was 7 Gy × 4 fractions to point A in all patients, corresponding to a prescribed dose of 84 Gy BED2Gy. Dose-volume histograms were calculated for the HR-CTV, rectum, bladder, and sigmoid colon. Optimization by adjustment of dwell weight and dwell time were performed for the dose distribution of HR-CTV, bladder, rectum and sigmoid colon according to GEC-ESTRO recommendations. The target and OARs doses were calculated into the equivalent dose in 2-Gy fractions (BED2Gy) using the linear-quadratic model and assuming α/β ratio = 10 for tumor and α/β = 3 for OARs.9) The prescribed dose was normalized using this formula and were denoted by Gy α/β3 (critical normal organs) or Gy α/β10 (target HR-CTV). The BED2Gy of the complete
EBRT and all brachytherapy fractions were added to evaluate the optimized plan with regard to the DVH constraints corresponding to a prescribed dose of at least 85 Gy BED$_{2\text{Gy}}$ to HR-CTV. Dose constraints for the OARs, total D$_{2\text{cc}}$ were $\leq 75$ Gy$_{\alpha/\beta}$ for rectum/sigmoid colon and $\leq 90$ Gy$_{\alpha/\beta}$ for the bladder, respectively. The acute toxicities were recorded by using the common terminology criteria of adverse events (CTCAE) version 3.0.

**RESULTS**

From February 2009 to March 2011, seventeen patients with locally advanced cervical cancer were included in the study. One patient refused the treatment and one patient stopped treatment due to psychological problems; 15 patients could be evaluated. The mean age was 53.6 years with the range of 35–63. A comparison of the tumor volume at diagnosis (GTV-Dx) and at the first brachytherapy (GTV-BT) revealed that 11 of 15 patients showed a tumor regression of more than 80% while only four patients had less than 80% of tumor regression. Table 1 depicts patient characteristics. The mean D$_{90}$ of HR-CTV and the cumulative D$_{2\text{cc}}$ of bladder, rectum, and sigmoid which were calculated from the summation of BED$_{2\text{Gy}}$ of EBRT and BT (mean ± standard deviation) were $99.2 \pm 11$ Gy, $87.7 \pm 5.7$ Gy, $68.4 \pm 5.4$ Gy and $70.3 \pm 6.8$ Gy, respectively. In comparison with BED$_{2\text{Gy}}$ of the standard plans at point A, image-based planning reduced the dose to OARs significantly. All data are shown in Table 2.

When we considered the dose at point A in all optimized plans, the mean dose at point A was 670.54 cGy (range: 371–2632 cGy). The mean doses of point AR and AL were 684.26 cGy (range: 373–2632 cGy) and 658.82 cGy (range: 374–1366 cGy), respectively.

After treatment completion, the three months evaluation MRI showed tumor persistence in six of 15 patients. Biopsy for histo-pathological confirmation was performed and showed negative results of malignancy. In addition, during the study time (at least six months of follow-up time) no
local recurrence was observed.

No patient developed grade 3–4 acute toxicities during treatment. The most common acute toxicities were anemia (four patients), leucopenia (four patients) and gastrointestinal toxicities (seven patients). Only one patient developed grade 2 acute toxicities in the anemia, leucopenia, and GI grouping. All acute toxicities were shown in Table 3. In

### Table 2. Comparison of dose parameters (mean D90 of HR-CTV, and D2cc of bladder, rectum, sigmoid) for the treatment of MRI-guided brachytherapy in locally advanced cervical cancer in term of \( \text{BED}_{2 \text{Gy}} \) – standard versus optimized plans

| Parameters       | Standard-plan mean dose in Gy (dose range) | Optimized-plan mean dose in Gy (dose range) | P-value |
|------------------|------------------------------------------|--------------------------------------------|---------|
| D90 HR-CTV       | 115.2 (85.9–150.5)                       | 99.2 (88.5–127)                            | 0.005   |
| D2cc bladder     | 127.7 (77.7–226.2)                       | 87.7 (76.6–94)                             | 0.003   |
| D2cc rectum      | 79.5 (61.4–120.8)                        | 68.4 (62.2–81.7)                           | 0.015   |
| D2cc sigmoid     | 85.2 (58.4–127.2)                        | 70.3 (55.7–78.5)                           | 0.012   |

### Table 3. Acute toxicity profile in 15 patients treated with MRI-guided brachytherapy

| Side effects     | Grade and number of patients with toxicity |
|------------------|-------------------------------------------|
| Anemia           | G1: 3                                     |
|                  | G2: 1                                     |
| Leucopenia       | G1: 3                                     |
|                  | G2: 1                                     |
| Thrombocytopenia | G1: 1                                     |
|                  | G2: 0                                     |
| Nephrotoxicity   | G1: 1                                     |
|                  | G2: 0                                     |
| GI                | G1: 6                                     |
|                  | G2: 1                                     |
| GU                | G1: 2                                     |
|                  | G2: 0                                     |
| Skin             | G1: 0                                     |
|                  | G2: 0                                     |
terms of late morbidity, no grade 3–4 toxicity was observed.

**DISCUSSION**

Recently, MRI-guided brachytherapy was addressed and tested in Europe and United States.\(^{10-13}\) According to the study of Pötter et al., the image-guided brachytherapy could improve local control and reduce treatment-related toxicity. Overall survival (OS) was 58%, and cancer-specific survival (CSS) was 68% at three years. In two different consecutive study periods, OS improved further from 53% to 64% (\(p = 0.03\)) and in CSS from 62% to 74% (\(p = 0.13\)) reflecting a learning curve. However, improvement occurred only in tumors greater than five cm: OS 28% versus 58% (\(p = 0.003\)) and CSS 40% versus 62% (\(p = 0.07\)). The actuarial late morbidity rate (grades 3 and 4) at three years was low with 4% for gastrointestinal and 4% for the urinary system, respectively.\(^{14}\)

In the years 2005 and 2006, the GEC-ESTRO published the recommendations of using image-guided brachytherapy in cervical carcinoma.\(^{5,6}\) By utilizing MRI-imaging, the concepts of target volumes (gross tumor volume, high-risk clinical target volume, intermediate-risk clinical target volume), of organs at risk (bladder, rectum and sigmoid), and dose constraints to these volumes were identified. The supportive data from Brabandere et al. analyzed sixteen patients with carcinoma of cervix after boost treatment with PDR brachytherapy. The x-ray based plan was projected to MRI. After target and OAR contouring, the DVHs of OARs and target volumes (HR-CTV) were evaluated and the plans were manually optimized using the MR information. The study showed an over dosage in D2cc of bladder (10/16) and sigmoid colon (7/16) and an under dosage of D90 of HR-CTV in 13/16 patients of X-ray based plans. After optimizing, the doses in the OAR were not peaking in all patients and average dose of HR-CTV increased. The authors concluded that MRI helped to reduce the dose to OARs and improved the target coverage.\(^{15}\) The study of Zwahlen et al., using MRI-guided brachytherapy for pulsed-dose-rate brachytherapy boost in the treatment for 20 patients of cervical cancer, showed that HR-CTV and IR-CTV were optimally treated in 70% and 85% of the patients with conventional plans, and in 75% and 95% of the patients with imaging-based optimized plans, respectively. Furthermore, the authors could demonstrate diminished minimal doses to the contiguous 2-cc of the rectum, sigmoid, and bladder of 12–32% difference in favor of 3D planning versus conventional BT planning.\(^{16}\)

Our study also demonstrated a clear advantage of image-guided brachytherapy with D90 of HR-CTV, D2cc of bladder, D2cc of rectum and D2cc of sigmoid of 99.8 ± 11 Gy, 87.5 ± 5.7 Gy, 68.8 ± 5.4 Gy and 70.2 ± 7.1 Gy, respectively. Although the dose to the HR-CTV was reduced by optimization, the equivalent dose BED\(_{2\text{Gy}}\) at D90 for HR-CTV could be preserved greater than or equal to 87 Gy according to the Vienna study,\(^{17}\) and the cumulative dose of D2cc of bladder, rectum and sigmoid could be substantially reduced. Moreover, 11 of 15 patients in our study showed longitudinally more than 80% tumor regression which demonstrated the benefit of the MRI to identify the residual tumor after the external beam radiotherapy and initiation of brachytherapy treatment. A prospective long-term follow-up program was planned to evaluate the results in the sense of a longitudinal survivorship trial, and efficacy of newly defined workflows. Two MRI machines in the hospital were used for this purpose. For the planning process, patients were transferred from our department (basement area) to the nearest MRI machine on the first floor by a patient dedicated elevator. After imaging was performed, patients were transferred back to the operating room. MRI imaging was also transferred to the treatment planning system (TPS). Then the planning process started. The registered workflow time from initiation to the end of the procedure was approximately three to four hours per patient in comparison with the conventional film-based planning of 0.5–1 hours. However, the planning procedure was generally well tolerated. Additional oral analgesia was only exceptionally required. Spinal anesthesia was needed only when the treatment included additional interstitial implantation. In 11 out of the total 60 applications, additional needle implantation was performed to improve the geometry. This specific technique helped to improve the conformality of D90 HR-CTV and reduce the D2cc of OARs especially in poor response cases after EBRT. However, the use of needles had consequences on planning, when needles had to be placed very close to point A. In these cases point A dose evaluation was not useful due to very high contact doses. The use of volume-based concepts was more reasonable. Caution is necessary, when needles are implanted too close to the OARs, which may cause high late morbidity due to very high contact doses. For the CT-planning phase (in 2nd to 4th applications), the total duration from initiation to the end of the process was approximately one to two hours.

In the present study, the utilization of MRI-guided brachytherapy enabled improvement of the dose distribution of HR-CTV and reduction of doses to the organs at risk. In the future, the implementation of inverse planning might be utilized. The study of Chajon et al. used inverse planning simulated annealing (IPSA) with PDR brachytherapy of 15 Gy to IR-CTV in 30 patients with cervical carcinoma. Compared with classic manual optimization, the mean D90, D100, and V100 calculated with both methods did not differ significantly. The authors concluded that the inverse planning method provided fast and automatic solutions for the optimization of dose distribution. However, the straightforward use of IPSA generated significant heterogeneity in dwell time values.\(^{18}\) Similar results were achieved by the study of DeWitt et al. The IPSA algorithm was applied in 15 patients treated with HDR brachytherapy for cervical
cancer using tandem and ovoid applicators. Better target volume coverage with equivalent doses to the bladder and rectum were obtained,\textsuperscript{19} Moreover, the study of Trnková, \textit{et al} and Jamema \textit{et al} showed that inverse optimization with the Hybrid Inverse Treatment Planning and Optimization (HIPO) algorithm offered good sparing of critical structures without compromising the target coverage when compared to standard loading and manual optimization in 28 patients.\textsuperscript{20,21}

In conclusion, by using GEC-ESTRO recommendations, target volumes and OARs could be accurately identified with the MRI. The MRI is valuable for the evaluation of the tumor response after EBRT and is very helpful for the prediction of prognosis by residual GTV evaluation. Furthermore, image-guided brachytherapy allowed us to optimize the dose for both target volumes and OARs. These early results with good tumor response in all enrolled patients and very low treatment-related morbidity support the usage of MRI for treatment planning and longitudinal evaluation. However, long-term data is needed to evaluate the overall benefit of this treatment modality.

ACKNOWLEDGEMENTS

This study was partially supported by the fund of the Faculty of Medicine, Chiang Mai University for the first five patients and Nucletron B.V., Veenendaal, The Netherlands for the remaining patients. Many thanks are expressed to numerous interdisciplinary co-operations with our institutional colleagues (e.g. Dr. Chate Sivasomboon, Radiology Department), our nurses, our physicists, our technicians, our department staff and many other project supporters within our entire institution.

REFERENCES

1. Rose PG, \textit{et al} (1999) Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 340: 1144–1153.
2. Keys HM, \textit{et al} (1999) Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med 340: 1154–1161.
3. Eifel PJ, \textit{et al} (2004) Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: An update of Radiation Therapy Oncology Group trial (RTOG) 90-01. J Clin Oncol 22: 872–880.
4. Perez CA, \textit{et al} (1986) Radiation therapy alone in the treatment of carcinoma of the uterine cervix: a 20-year experience. Gynecol Oncol 23: 127–140.
5. Haie-Meder C, \textit{et al} (2005) Recommendations from Gynecological (GYN) GEC-ESTRO Working Group (I): Concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Radiother Oncol 74: 235–245.
6. Pötter R, \textit{et al} (2006) Recommendations from gynecological (GYN) GEC ESTRO working group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol 78: 67–77.
7. Viswanathan AN, \textit{et al} (2007) Computer tomography versus magnetic resonance image-based contouring in cervical cancer brachytherapy: Result of a prospective trial and preliminary guidelines for standard contours. Int J Radiat Oncol Biol Phys 68: 491–498.
8. Taylor A, \textit{et al} (2005) Mapping pelvic lymph nodes: Guidelines for delineation in intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 63: 1604–1612.
9. Joiner MC and Bentzen SM (2002) Time-dose relationships. The linear-quadratic approach. In: Steel GG, ed. Basic Clinical radiobiology. pp. 120–133. Arnold; London.
10. Pötter, \textit{et al} (2008) Present status and future of high-precision image guided adaptive brachytherapy for cervix carcinoma. Acta Oncol 47: 1325–1336.
11. Pötter, \textit{et al} (2009) Image-guided brachytherapy sets benchmarks in advanced radiotherapy. Radiother Oncol 91: 141–146.
12. Tanderup K, \textit{et al} (2010) Adaptive management of cervical cancer radiotherapy. Semin Radiat Oncol 20: 121–129.
13. Viswanathan AN and Erickson B (2010) Three-dimensional imaging in gynecologic brachytherapy: a survey of the American brachytherapy society. Int J Radiat Oncol Biol Phys 76: 104–109.
14. Pötter R, \textit{et al} (2007) Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. Radiat Oncol 83: 148–155.
15. Brabandere MD, \textit{et al} (2008) Potential of dose optimisation in MRI-based PDR brachytherapy of cervix carcinoma. Radiother Oncol 88: 217–226.
16. Zwahlen D, \textit{et al} (2009) Magnetic resonance imaging-guided intracavitary brachytherapy for cancer of the cervix. Int J Radiat Oncol Biol Phys 74: 1157–1164.
17. Dimopoulos JC, \textit{et al} (2009) Dose-effect relationship for local control of cervical cancer by magnetic resonance image-guided brachytherapy. Radiother Oncol 93: 311–315.
18. Chajon E, \textit{et al} (2007) Inverse planning approach for 3-D MRI-based pulse-dose rate intracavitary brachytherapy in cervix cancer. Int J Radiat Oncol Biol Phys 69: 955–961.
19. DeWitt K, \textit{et al} (2005) 3D inverse treatment planning for the tandem and ovoid applicators in cervical cancer. Int J Radiat Oncol Biol Phys 63: 1270–1274.
20. Trnková P, \textit{et al} (2009) New inverse planning technology for image-guided cervical cancer brachytherapy: description and evaluation within a clinical frame. Radiother Oncol 93: 331–340.
21. Jamema SV, \textit{et al} (2010) Comparison of DVH parameters and loading patterns of standard loading, manual and inverse optimization for intracavitary brachytherapy on a subset of tandem/ovoid cases. Radiother Oncol 97: 501–506.

Received on June 19, 2011
Revision received on October 5, 2011
Accepted on October 20, 2011
J-STAGE Advance Publication Date: January 21, 2012