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Intermediate-term results of image-guided brachytherapy and high-technology external beam radiotherapy in cervical cancer: Chiang Mai University experience

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HIGHLIGHTS

- Image-guided brachytherapy showed promising intermediate-term results in the treatment of cervical cancer.
- Image-guided brachytherapy caused a low incidence of grade 3–4 toxicity in treated study patients.

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ABSTRACT

Objective. To evaluate the outcomes of image-guided brachytherapy combined with 3D conformal or intensity modulated external beam radiotherapy (3D CRT/IMRT) in cervical cancer at Chiang Mai University.

Methods. From 2008 to 2011, forty-seven patients with locally advanced cervical cancer were enrolled in this study. All patients received high-technology (3D CRT/IMRT) whole pelvic radiotherapy with a total dose of 45–46 Gy plus image-guided High-Dose-Rate intracavitary brachytherapy 6.5–7 Gy × 4 fractions to a High-Risk Clinical Target Volume (HR-CTV) according to GEC-ESTRO recommendations. The dose parameters of the HR-CTV for bladder, rectum and sigmoid colon were recorded, as well as toxicity profiles. In addition, the endpoints for local control, disease-free, metastasis-free survival and overall survival were calculated.

Results. At the median follow-up time of 26 months, the local control, disease-free survival, and overall survival rates were 97.9%, 85.1%, and 93.6%, respectively. The mean dose of HR-CTV, bladder, rectum and sigmoid were 93.1, 88.2, 69.6, and 72 Gy, respectively. In terms of late toxicity, the incidence of grade 3–4 bladder and rectum morbidity was 2.1% and 2.1%, respectively.

Conclusions. A combination of image-guided brachytherapy and IMRT/3D CRT showed very promising results of local control, disease-free survival, metastasis-free survival and overall survival rates. It also caused a low incidence of grade 3–4 toxicity in treated study patients.

Introduction

Cervix carcinoma is one of the most frequent cancer entities in Northern Thailand. According to the report of Kamnerdsupaphon et al., the age-standardized incidence rates were 22.7 and there were 234 new cases of cervix cancer diagnosed in 2005 [1].

The treatment options of cervical cancer are composed of surgery, radiotherapy and chemotherapy according to the stage and performance status of the patients. Radiotherapy plays an important role in early and advanced stages of the disease. For early disease, radical radiotherapy is a good alternative option to surgery for medically operable patients. For locally advanced disease, radical radiochemotherapy is the standard treatment, and combined modalities improve treatment results [2–4].

Radical radiotherapy constitutes external beam radiotherapy (EBRT) and brachytherapy (BT). EBRT (45–50.4 Gy) aims to reduce gross tumors and control microscopic disease in the pelvic area, while BT is used to boost the dose to the local lesion up to 75–90 Gy.

For conventional brachytherapy planning, simple orthogonal X-rays are usually obtained to evaluate the position of the applicator in relation to musculoskeletal pelvic anatomy and the dose is prescribed to a fixed reference point 2 cm superior and 2 cm lateral to the distal end of the applicator/tandem (Point A), regardless of tumor characteristics or the individual patient anatomy [5]. Computed tomography (CT) or MRI (magnetic resonance imaging) is increasingly used in the diagnosis/staging of cervical cancer [6]. Errors in clinical staging have been reported in up to 22% of patients with stage I disease and in up

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to 75% with stage III disease. These errors arise from a failure to recognize infiltration of the parametrium, the pelvic sidewall, or the bladder/rectal wall and metastatic spread. CT and MRI can aid in the staging and follow-up of patients with advanced cervical cancer [7]. In this new era of advanced imaging technology, therefore, Gross Tumor Volume (GTV) or Clinical Target Volume (CTV) and organs at risk (bladder, rectum and others) can be superiorly identified. Schöppel et al. reported the use of magnetic resonance imaging (MRI) for brachytherapy in cervical cancer in 1992 [8] when the concept of image-guided brachytherapy was developed. With the emergence of Groupe Européen de Curiethérapie — European Society for Therapeutic Radiology and Oncology (GEC-GESTRO) recommendations, volume-based tumor concepts (Gross Tumor Volume; GTV and Clinical Target Volume; CTV) for organs at risk (bladder, rectum and sigmoid colon) with dose constraints in terms of Dose-volume-histograms (DVHs) have significantly improved brachytherapy in the treatment of cervical cancer [9,10]. After the preliminary results of IGBT for cervical cancer by Pötter et al. were reported [11], the concepts of IGBT were addressed by other research groups. Many studies reported the disadvantages of X-ray based planning in the treatment of cervical cancer by using brachytherapy in the modern imaging era [12–15]. Additionally, previous preliminary studies from our group at Chiang Mai University in Thailand showed that image (CT/MRI)-based brachytherapy could reduce the dose to OARs significantly (except for rectum in CT-based brachytherapy) while maintaining target dose coverage in comparison to standard planning in terms of EQD2, according to GEC-ESTRO recommendations [16,17]. All data supports the use of image-guided brachytherapy (IGBT) and volume-based planning in clinical practice. However, the developments of modern radiotherapy techniques such as IGBT, and their potential benefits, should be further tested. Our division had started this prospective project of image-guided brachytherapy in 2008. Evaluation of the continued results of newly introduced IGBT remains essential at longer follow-up periods. Thus, we performed this study to evaluate the long term results and treatment-related toxicities of image-guided (with CT or MRI) brachytherapy in cervical carcinoma and we focused on a prospective approach for locally advanced cervical cancer (FIGO IIB–IIIB), which may potentially benefit the most from these technology advances.

Materials and methods

Patients

After approval of the institutional review board, forty-seven patients with carcinoma of cervix uteri from July 2008 to December 2011were included in this study. All cervical cancer patients were classified as IIB and IIIB using FIGO clinical staging, were at ages ranging from 18 to 70 years old, and had a Karnofsky performance status > 70%. Patients with a severe co-morbidity, an emergency condition (e.g. bleeding that could not allow for treatment initiation thereby causing delay and a complex planning process), pregnancy, previous irradiation or history of allergies were excluded from the study. Informed consents were signed by all patients before treatment.

All patients received whole pelvis irradiation with 3D conformal radiotherapy (3D CRT) or intensity-modulated radiation therapy (IMRT) to a total dose of 45–46 Gy in 23–25 fractions. In 3D-CRT, a parametrial boost to 50.4–56 Gy was considered individually when parametrial involvement was found per vaginal examination after the fourth week of EBRT. For IMRT, the dose of 45 Gy in 25 fractions was prescribed to the dose at 98% of clinical target volume (CTV). CTV was defined as an area of potential microscopic disease and included the Gross Tumor Volume, whole cervix, entire uterus, parametrial tissue, and the upper vagina [18,19]. The pelvic lymph node groups (common iliac nodes, external iliac nodes, internal iliac nodes, obturator nodes, and pre-sacral lymph nodes) were identified and included to the CTV [20,21].

Concomitant radiochemotherapy

Concomitant radiochemotherapy with weekly cisplatin doses of 40 mg/m^2 for a maximum of six courses was given to patients with sufficient kidney and bone marrow function. Complete blood counts and renal function tests (serum blood urea nitrogen and creatinine) were evaluated weekly before consideration of chemotherapy. The dose of chemotherapy was modified according to a weekly assessment of creatinine clearance prior to each applied dose. Chemotherapy was held back when creatinine clearance was less than 40 ml/min, and considered to be stopped when creatinine clearance was less than 30 ml/mn.

Brachytherapy

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 6.5–7 Gy per fraction (with a total of four fractions) to High-Risk Clinical Target Volume (HR-CTV) was applied as per the routine prescribed schedule of the division of therapeutic radiology and oncology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand [22]. Standard tandem/ovoid or CT/MR applicators were used. A Foley's catheter was placed in the bladder and filled 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 for imaging planning. 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 imaging devices, 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 the MRI and CT scans was 5 mm without an interslice 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. Computed tomography or magnetic resonance imaging was used and GEC-ESTRO definitions were applied to identify target volumes e.g. Gross Tumor Volume (GTV) or High-Risk Clinical Target Volume (HR-CTV), and organs at risk (OARs) [9,10,23]. Dose-volume histograms were calculated to consider the adequate dose to HR-CTV and limitations of OARs. The D90 (minimum dose covering 90% of 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 to HR-CTV was 6.5–7 Gy × 4 fractions. Dose-volume histograms were calculated for the HR-CTV, rectum, bladder, and sigmoid colon. Optimization by adjustment of dwell weight and dwell time was performed for the dose distribution of HR-CTV, bladder, rectum and sigmoid colon according to GEC-ESTRO recommendations. The cumulative target and OAR doses (EBRT plus IGBT) were calculated to the equivalent dose in 2-Gy fractions (EQD2) using the linear-quadratic model and assuming α/β ratio = 10 for the tumors and $\alpha/\beta = 3$ for OARs [24].

Outcomes

After the treatment was completed, patients were appointed to visits for vaginal examination (PV exam) in a follow-up program. The follow-up program schedule was performed every 3 months in the first 3 years after treatment was finished. In the 4th–5th year, the appointment was every 6 months and then annually after the 5th year. A vaginal examination was performed to evaluate the disease status according to World Health Organization (WHO) criteria. Investigations