

RESEARCH ARTICLE

Treatment Interruption During Concurrent Chemoradiotherapy of Uterine Cervical Cancer; Analysis of Factors and Outcomes**Srichai Krusun, Montien Pesee*, Narudom Supakalin, Komsan Thamrongnantasakul, Chunsri Supaadirek, Prawat Padoongcharoen****Abstract**

Background: To evaluate factors which effect treatment interruption during concurrent chemoradiotherapy (CCRT) and overall survival in patients with uterine cervical cancer stage IB2-IVA in Srinagarind Hospital. **Materials and Methods:** Between January 2006 and December 2007, 107 patients with stage IB2-IVA as FIGO staging, 2000, were treated with CCRT in Srinagarind Hospital. Factors which caused treatment interruptions and impacted on overall survival were reviewed and analyzed. **Results:** Twenty of 107 patients had treatment interruption during CCRT in patients with uterine cervical cancer stage IB2-IVA in Srinagarind Hospital. The causes of treatment interruption were as follows: hematologic toxicity was found in 16 of 20 cases, 12 cases with grade 2 and 4 cases with grade 3; three of 20 cases had gastrointestinal toxicities, 1 case with grade 2 and 2 cases with grade 3; one case had grade 3 skin toxicity. The mean total treatment time of the uninterrupted and interrupted groups were significantly different (78.98 days vs 161.80 days, $p < 0.001$). The patients who could tolerate ≥ 5 cycles of cisplatin administration had significantly higher mean white blood counts (WBC) ($9,769 \text{ cells/mm}^3$ vs $7,141 \text{ cells/mm}^3$, $p=0.02$). The mean initial hemoglobin (Hb) in the uninterrupted group was significantly higher than the interrupted group (11.5 mg\% vs 10.3 mg\% , $p=0.03$). Other factors including age, KPS, initial platelets, initial serum creatinine levels showed no statistical significance. The 3-year overall survival of the uninterrupted group was better than in the interrupted group (78.6% vs 55.0% , $p=0.03$). **Conclusions:** The initial Hb and WBC levels were significantly correlated with treatment interruption during CCRT in patients with uterine cervical cancer. The 3-year overall survival of the uninterrupted group was significantly better than interrupted group. These factors may then be used indirectly to predict the outcomes of treatment.

Keywords: Treatment interruption - uterine cervical cancer - concurrent chemoradiotherapy - factors - outcomes

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Introduction

The age standardized rate (ASR) of cervical cancer of the southwest Iran was found to be 2.56 per 100,000 person-years (Talaiezhadeh et al., 2013). In Osaka, Japan, the ASR of cervical cancer was 12.3 per 100,000 person-years (Utada et al., 2012). While, the ASR of cervical cancer in Thailand was 20.9 per 100,000 person-years (Deerasamee and Srivatanakul, 1999). The incidence of cervical cancer in Khon Kaen province was 14.6% of all female cancers (Cancer unit KKU., 2008), making it the most common cancer among women. Meanwhile, 70-90% of these patients presented with advanced stage disease. For stage I disease, cure rates approached almost 90%, but survival decreased with more advanced disease, especially in patients with bulky tumors (Tungsubutra et al., 1985; Arai et al., 1992; Pesee et al., 1995; Lorvidhaya et al., 2000; Wong et al., 2003; Pomros et al., 2007; Rose et al., 2007; Pesee et al., 2010; Potter et al., 2011; Intaraphet et al., 2013; Pesee et al., 2013). In addition, the cost of

treatment in cervical cancer depends on the stages of disease (Berraho et al., 2012).

The current standard treatment of cervical cancer FIGO (2000) stage IB2-IVA is concurrent cisplatin-based chemoradiotherapy (NCI, 1999; Rose, 2000). Cisplatin was hypothesized to have radiosensitizing activity when used concurrently with radiotherapy. There are proposed mechanisms of the radiosensitizing effects that include inhibition of repair of potential lethal or sublethal damage and increased radiosensitivity of hypoxic cells to radiation. A Gynecologic Oncology Group (GOG) protocol-120 showed that weekly intravenous 40 mg/m² cisplatin for 6 weeks in combination with radiation was effective, well tolerated and quite convenient. Several studies demonstrated more treatment toxicity in patients who were treated with CCRT than with radiotherapy alone (Kirwan et al., 2009). The most common toxicities were hematologic and gastrointestinal. Treatment toxicities sometimes caused treatment interruption and prolonged the overall treatment time (Monk et al., 2007). The effect of

prolonged treatment time had been proven to be associated with decreased local control and overall survival in cervical cancer (Petereit et al., 1995).

The aim of this study was to evaluate the factors which affected treatment interruption and overall survival in patients with uterine cervical cancer stage IB2-IVA treated with CCRT in Srinagarind Hospital.

Materials and Methods

Between January 2006 and December 2007, 144 patients with a diagnosis of cervical cancer FIGO 2000, stage IB2-IVA (Benedet et al., 2000) were treated with CCRT in Srinagarind Hospital. Only 107 patients treated with weekly intravenous cisplatin at a dose of 40 mg/m² concurrent with pelvic irradiation were enrolled in this study. The other 37 patients who were treated with other regimens were excluded.

The inclusion criteria for using CCRT in the patients with cervical cancer were FIGO 2000, (Benedet et al., 2000) stage IB2-IVA, an age < 60 years, Karnofsky performance status (KPS) ≥ 60%, adequate bone marrow function (ANC ≥ 1,500 cells/mm³, a platelet count ≥ 100,000 cells/mm³), good renal function with serum creatinine ≤ 1.5 mg/dl and a calculated glomerular filtration rate (GFR) ≥ 50 ml/min., no ureteric obstruction and adequate liver function (McArdle and Kigula-Mugambe, 2007). The patients who were pregnant, had human immunodeficiency virus (HIV) infection, a previous hysterectomy, distant metastases, an active serious infection and underlying diseases expected to be chemointolerant were excluded from this study. Data were collected from the medical records, histological reports, and the tumor registry. All patients were divided into two groups, the first was without treatment interruption (uninterrupted group) and the second had treatment interruption (interrupted group).

Treatment-related complications were recorded and categorized according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. General criteria for treatment interruption were ≥ grade 2-3 toxicities, eg. hematologic, gastrointestinal, renal, skin, mucosal toxicities and poor performance (KPS < 60%). During CCRT, the treatments would be interrupted if the KPS < 60%, ANC < 1,500 cells/mm³, a platelet count < 100,000 cells/mm³, serum creatinine > 1.5 mg/dl and GFR < 50 ml/min, severe complications or uncontrolled infection. The reasons for interruption of treatment in both groups were reviewed from the medical records. The living status of the patients was obtained from the department of provincial administration, Ministry of Interior, Thailand. The overall survival rate (OS) was calculated from the first date of treatment to the date of death or last documented follow-up visit.

This study has been approved by the Human Ethics Committee of Khon Kaen University (HE531312).

Radiotherapy

All patients were treated with a combination of external beam radiation therapy (EBRT) and Ir-192 high-dose-rate vaginal brachytherapy (HDR VBT). The radiation treatment consisted of whole pelvic irradiation

with a total dose of 5,000 cGy/5weeks, 1.8-2.0 Gy/fraction. In this study, 104 patients were treated with antero-posterior irradiation fields and only 3 patients with the four-field technique (box technique).

The target volume for EBRT was defined to include the tumor, the upper two thirds of vagina and the pelvic lymph nodes. The para-aortic lymph nodes were not included in the treatment fields. The superior border was placed at the L5-S1 interspace, the inferior border was at the inferior margin of the obturator foramen or below the involved vaginal margin plus 2 centimeters depending on which one was lower. The lateral borders were placed at widest opening of bony pelvis plus 1.5-2.0 centimeters. For the lateral fields, the superior border was placed at the L5-S1 interspace, the inferior border was at the inferior margin of the obturator foramen or below the involved vaginal margin plus 2 centimeters depending on which one was lower. The anterior margin was posterior to the pubic symphysis and the posterior border was at the junction of 2nd-3rd sacral bones. Midline shields were usually applied in cases with a tumor size ≤ 3 cm. at a total dose of 4000 cGy. After midline shielding or completion of EBRT, four sessions of HDR VBT were applied one week apart with radiation doses of 600-650 cGy/fraction at point A. The applicators used for VBT were Heinschke applicators. The parametrial boost by small radiation fields were sometimes added in cases of gross involvement with 600-1,000 cGy radiation doses. Hence, the total equivalent dose with a 200 cGy/fraction at point A (ICRU 38) was 8,000-9,000 cGy.

The overall treatment time was calculated from the first day of treatment until the last day of HDR VBT. The complications during the treatment course were recorded and categorized by using CTCAE V3.0 criteria.

Chemotherapy (CMT)

Cisplatin (40 mg/m²) was given intravenously once a week concurrent with radiotherapy. Before administration of cisplatin, the patients must have been prehydrated with 2,000 ml of 5% dextrose in half-strength saline by an intravenous infusion approximately for 12 hours over night beforehand. The weekly dose of cisplatin was 40 mg/m² and calculated by body surface area, but could not exceed 2.0 m². The toxicities were monitored by gynecologic oncologists. Chemotherapy was given intravenously on the basis of weekly doses from the first day of radiation therapy until the external radiation was completed.

During CCRT, the weekly cisplatin was stopped if the patients had a certain degree of toxicity from cisplatin such as an ANC < 1,500 cells/mm³, a platelet count < 100,000 cells/mm³, a serum creatinine > 1.5 mg/dl, a glomerular filtration rate (GFR) < 50 ml/min, poor performance status (KPS < 60%), severe neurologic toxicity or refused chemotherapy. The patients were followed periodically by the radiation oncologists and gynecological oncologists. The complications after complete treatment were evaluated and recorded.

Statistical analysis

Pearson chi-squared and Fisher exact tests were used

for independent variable factors. Analyses of survival parameters were carried out by the Kaplan-Meier method and Log-rank tests. All data were evaluated using the STATA versions 10.1 software package. A p-value of ≤ 0.05 was considered statistically significant.

Results

Between January 2006 and December 2007, there were 445 patients with a diagnosis of uterine cervical cancer stage IB2-IVa. From these patients, 144 patients were treated by CCRT, but only 107 patients were enrolled in this study because the other 37 patients received another regimen of chemotherapy. The patient characteristics are summarized in Table 1.

The mean total radiation dose at point A was approximately 8,887 cGy (range 7,500-11,800 cGy). Complications were found in 43 cases (40.2%). The

major complications were hematologic toxicity in 23 cases (21.5%) and gastrointestinal toxicity in 19 cases (17.8%). The other complications were renal toxicity, 2 cases (1.9%), skin toxicity, 1 case (0.9%) and hepatitis, 1 case (0.9%).

Of all 107 cases, there were 20 cases that had interruption of radiation due to toxicity of the treatment. The grade 2 hematologic toxicities were found in 12 cases (11.21%) and grade 3 were found in 4 cases (3.74%). The grade 2 gastroduodenal toxicity was found in 1 case (0.93%) and grade 3 was in 2 cases (1.87%). The grade 3 skin toxicity was found in 1 case (0.93%). So, the majority of toxicities which caused interruption of treatment were hematologic toxicities (80%).

The mean total treatment time (EBRT plus HDR VBT) was 83.24 days (range 55-177 days). The median follow-up time was 891 days. In subgroup analysis, the mean age in the uninterrupted group was 47.09 years while in the interrupted group was 50.30 years ($p=0.08$). The mean total treatment time of the uninterrupted and interrupted groups were 78.98 days and 161.80 days with statistical significance ($p < 0.001$). The mean initial Hb levels in the uninterrupted group and interrupted groups were 11.53 mg% and 10.30 mg%. In univariate analysis, there was a significant difference in the initial Hb levels between the two groups ($p=0.03$) as shown in Table 2. Other factors including age, KPS, initial WBC and ANC, initial platelets, initial serum creatinine were not statistically significant between the groups. The 75% of survival of patients in the uninterrupted group was 1,114 days while in interrupted group was 495 days ($p=0.03$).

The cycles of chemotherapy ranged from 2-6 cycles. There were 17/107 cases that received fewer than 5 cycles of cisplatin (15.89%), and 7 cases had interrupted radiation and stopped weekly cisplatin due to grade 2-3 hematologic toxicity. Six cases had to stop weekly cisplatin due only to its toxicity, but the radiation therapy still continued. Other

Table 1. Patient Characteristics

| Characteristics | Mean (Range) | SD |
|------------------------------|----------------------|----------|
| Age (years) | 47.64 (28-65) | 8.14 |
| KPS (%) | 87.38 (70-100) | 5.84 |
| Size (cm) | 4.93 (1.5-12.0) | 1.90 |
| Hb (mg%) | 11.30 (5.3-16.0) | 1.98 |
| WBC (cells/mm ³) | 9,478 (3,800-26,000) | 3,645.15 |
| ANC (cells/mm ³) | 6,817 (2,540-8,844) | 836.70 |
| Chemotherapy (cycles) | 5 (2-6) | 0.94 |

| Histology | Cases | Percent |
|-------------------------|-------|---------|
| Squamous cell carcinoma | 78 | 72.90 |
| Adenocarcinoma | 26 | 24.30 |
| Small cell carcinoma | 1 | 0.90 |
| Others | 2 | 1.90 |

| Stage | Cases | Percent |
|-------|-------|---------|
| IIA | 2 | 1.90 |
| IIB | 56 | 52.30 |
| IIIA | 2 | 1.90 |
| IIIB | 45 | 42.10 |
| IVA | 2 | 1.90 |

Table 2. Patient Characteristics between Uninterrupted Group (UG) and Interrupted Group (IG)

| Characteristics | Groups | Cases | Mean | SD | p value |
|------------------------------------|--------|-------|------------|------------|---------|
| Age(Yrs) | UG | 87 | 47.03 | 8.27 | 0.08 |
| | IG | 20 | 50.30 | 7.10 | |
| KPS(%) | UG | 87 | 87.82 | 5.32 | 0.11 |
| | IG | 20 | 85.50 | 7.59 | |
| Hb(mg%) | UG | 87 | 11.53 | 1.85 | 0.03 |
| | IG | 20 | 10.30 | 2.26 | |
| WBC (cells/mm ³) | UG | 87 | 9,614.37 | 3835.37 | 0.32 |
| | IG | 20 | 8,890.00 | 2663.97 | |
| ANC (cells/mm ³) | UG | 87 | 7,084.43 | 920.86 | 0.20 |
| | IG | 20 | 5,653.85 | 2233.64 | |
| Platelets (cells/mm ³) | UG | 87 | 361,172.41 | 119,103.64 | 0.88 |
| | IG | 20 | 355,850.00 | 146,170.87 | |
| Creatinine (mg%) | UG | 87 | 0.81 | 0.16 | 0.59 |
| | IG | 20 | 0.84 | 0.16 | |
| AST(U/L) | UG | 87 | 23.20 | 13.16 | 0.72 |
| | IG | 20 | 22.30 | 9.07 | |
| ALT(U/L) | UG | 87 | 22.95 | 12.69 | 0.13 |
| | IG | 20 | 19.45 | 8.23 | |
| ALP(U/L) | UG | 87 | 70.49 | 28.25 | 0.92 |
| | IG | 20 | 71.10 | 21.30 | |
| Total treatment time (Days) | UG | 87 | 78.98 | 22.01 | <0.001 |
| | IG | 20 | 101.80 | 16.06 | |

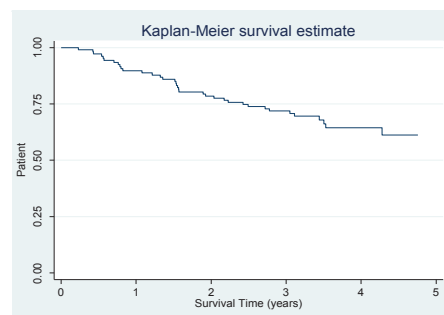


Figure 1. Overall Survival Rate

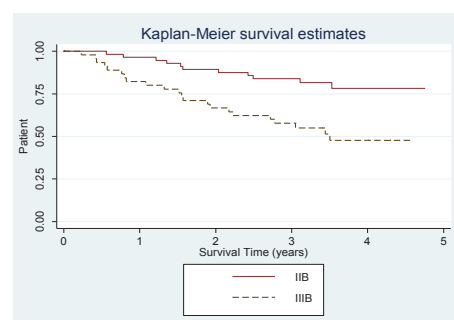


Figure 2. Overall Survival by Staging

toxicities were nephrotoxicity in 2 cases, hepatitis in 1 case and patients who could not tolerate to chemotherapy in 3 cases. Four cases refused chemotherapy.

In univariate analysis, the mean initial WBC levels between the cases who could tolerate <5 cycles of cisplatin and ≥5 cycles, were statistically significant (7,141 cells/mm³ and 9,769 cells/mm³) (p=0.02) as shown in Table 3. The other factors including age, KPS, initial Hb level, initial platelet level, initial serum creatinine and initial serum liver enzymes were not statistically significant between the groups.

Kaplan-Meier models were used to estimate overall survival. The 3-year overall survivals (3-yr OS) were

found to be 66/107 cases (61.68 %) as shown in Figure 1. The 3-yr OS according to stages IIB and IIIB were 83.93% and 57.78% as shown in Figure 2. For stages IIA, IIIA and IVA, the 3-yr OS could not be calculated because of the small number of cases. The 3-yr OS between uninterrupted and interrupted groups were statistically significant at 63.29% and 55.00% (p=0.03) as shown in Figure 3. In the cases who received <5cycles and ≥5 cycles of chemotherapy the differences in 3-yr OS were 64.71 % and 73.33%, which were statistically significant (p=0.04) as shown in Figure 4.

Discussion

The standard of care for locally advanced cervical cancer was the combination of EBRT plus HDR VBT and chemotherapy with cisplatin. In the systematic review of 19 randomized controlled trials studied by Green JA et al. (2001) the findings suggested that chemoradiation improved overall survival. There were more grade 3 and 4 hematologic and gastrointestinal toxicities in the CCRT group than in the control group. This study showed grade 2 and 3 hematologic toxicities of 12.10% and 2.8 %, while grade 2 and 3 gastrointestinal toxicities were 2.8% and 1.9%. Hematotoxicity was the major cause of treatment interruption and significant prolonged treatment time in the CCRT group in this study.

Perez et al. (1995) studied 1,224 cases with a diagnosis of uterine cervical carcinoma and that were treated with definitive radiation therapy. They found that interruptions of therapy accounted for prolongation of overall treatment time and significantly resulted in decreased pelvic tumor control and cause-specific survival. In this study, the overall survival in interrupted group was decreased significantly as compared with the uninterrupted group (p=0.03).

Obermair et al. (2003) demonstrated that the nadir hemoglobin (Hb) level was the most predictive factor for treatment failure (p=0.01), whereas the Hb level at the time of presentation was not of statistical significance. In this study, the mean initial Hb level in the interrupted group was significantly lower than in the uninterrupted group (p=0.01) from which it could be implied that the lower initial Hb level corresponded to interruption of treatment causing prolongation of total treatment time.

Nugent et al. (2010) reviewed 119 patients diagnosed with locally advanced cervical carcinoma who were treated with concurrent weekly administered cisplatin at 40 mg/m² and radiation therapy. They found that the patients who received <5 cycles of cisplatin were associated with decreased overall survival that was statistically significant as compared with patients who received >5 cycles of cisplatin (p<0.001).

In this current study, the overall survival in patients who received <5 cycles of cisplatin was decreased significantly (p=0.04) and the mean initial WBC level in the patients who received <5 cycles cisplatin was significantly (p=0.02) lower than of the patients who received ≥5 cycles cisplatin. Moreover, the patients with lower initial WBC levels tended to have an incomplete chemotherapy schedule. This study, however, has

Table 3. Patient characteristics between < 5 and ≥ 5 cycles of cisplatin cases

| Characteristics | CMT cycles | Cases | Mean | SD | p-value |
|------------------------------------|------------|-------|------------|------------|---------|
| Age(yrs) | CMT<5 | 17 | 48.35 | 7.69 | 0.69 |
| | CMT≥5 | 90 | 47.51 | 8.25 | |
| KPS(%) | CMT<5 | 17 | 85.29 | 6.24 | 0.14 |
| | CMT≥5 | 90 | 87.78 | 5.71 | |
| Hb(mg%) | CMT<5 | 17 | 10.44 | 2.52 | 0.13 |
| | CMT≥5 | 90 | 11.46 | 1.83 | |
| WBC(cells/mm ³) | CMT<5 | 17 | 7,941.18 | 2,507.25 | 0.02 |
| | CMT≥5 | 90 | 9,769.44 | 3,762.71 | |
| ANC(cells/mm ³) | CMT<5 | 17 | 5,059.71 | 2,154.15 | 0.06 |
| | CMT≥5 | 90 | 7,148.97 | 904.68 | |
| Platelets (cells/mm ³) | CMT<5 | 17 | 346,941.18 | 86,557.40 | 0.54 |
| | CMT≥5 | 90 | 362,677.78 | 129,950.97 | |
| Creatinine(mg%) | CMT<5 | 17 | 0.83 | 0.15 | 0.70 |
| | CMT≥5 | 90 | 0.81 | 0.16 | |
| AST(U/L) | CMT<5 | 17 | 23.35 | 13.87 | 0.92 |
| | CMT≥5 | 90 | 22.97 | 12.27 | |
| ALT(U/L) | CMT<5 | 17 | 27.18 | 19.15 | 0.24 |
| | CMT≥5 | 90 | 21.38 | 10.05 | |
| ALP(U/L) | CMT<5 | 17 | 81.59 | 39.36 | 0.07 |
| | CMT≥5 | 90 | 68.53 | 23.71 | |

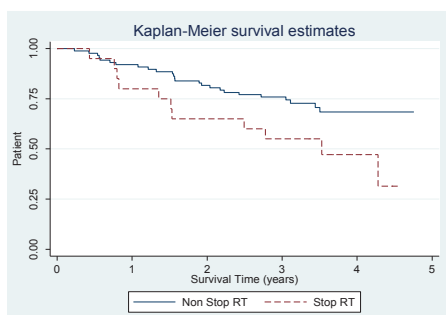


Figure 3. Overall Survival between Uninterrupted and Interrupted Groups

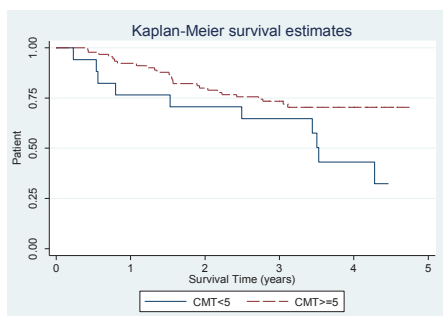


Figure 4. Overall Survival between Chemotherapy < 5 and ≥ 5 Cycles

limitations, due to its nonrandomized retrospective study design with a rather small number of patients. A further randomized study with larger numbers of patients is still needed. Proper selection of patients, however, with good supportive care during treatment may help the patients to be more tolerant to treatment with fewer interruptions and better results.

In conclusion, prolonged total treatment time and an incomplete course of CCRT were associated with decreased overall survival. From this study, the initial Hb level and initial WBC levels were the only factors that showed significant correlations to the tolerance of patients to CCRT in treatment of locally advanced uterine cervical carcinoma. These factors may be used to predict the treatment outcomes indirectly.

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