PROPHYLACTIC PARA-AORTIC RADIOTHERAPY AND CONCOMITANT CHEMOTHERAPY FOR PATIENTS WITH CERVICAL CARCINOMA: PRELIMINARY ANALYSIS OF OUTCOME AND TOXICITY

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Purpose *:* This study was to analyze the preliminary survival outcomes and treatment-related toxicities of definitive radiotherapy with prophylactic para-aortic irradiation and concurrent chemotherapy for patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIB/IIIB cervical carcinoma.

Materials and Methods *:* From June 1998 to June 2001, 20 patients with FIGO stage IIB or IIIB cervical carcinoma with no lymph node metastasis to the para-aortic area were included in the study. Patients were treated with definitive pelvic and prophylactic para-aortic radiotherapy, concomitant chemotherapy, and post-radiation chemotherapy. Radiation treatments included external radiation to the para-aortic area with 45 Gy in 25 fractions and to the whole pelvis with 50.4 Gy in 28 fractions, additional boost to the parametrium with 9 Gy in 5 fractions, and the intracavitary brachytherapy with point A doses of 22-30 Gy in 4-5 fractions. Chemotherapy included 2 cycles of cisplatinum 60-80 mg/m^2 on day 1 and day 29 during radiotherapy, and 2 cycles of cisplatinum 60-80 mg/m^2 and 5-fluorouracil 600-800 mg/m^2/day for 5 days, at 1 and 2 months after completion of radiotherapy. Patients were followed on a regular basis. The survival outcome was calculated by Kaplan-Meier method, and the treatment-related side effects were evaluated by RTOG criteria. The median follow-up interval was 15 months.

Results *:* All patients completed the planned radiotherapy and the planned 2 cycles of chemotherapy during radiotherapy. Sixteen patients (80%) underwent 2 cycles of the post-radiation chemotherapy, while 4 of them had modification of chemotherapy regimens. One patient had local recurrence, with the 2-year local control rate of 83%. None of the 20 patients had para-aortic recurrence, but one patient developed lung metastasis. All patients were alive and the 2-year survival rate was 100%. Most treatment-related side effects were gastrointestinal and hematological reactions. No patient had grade IV acute toxicity. For gastrointestinal toxicity, there were four patients (20%) with grade III reaction. For hematological toxicity, there were five patients (25%) with grade III reaction. All but 2 patients had the late toxicities less than or equal to grade II. No patient had the interruption of radiation therapy due to the treatment-related adverse effects.

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Conclusion : Definitive radiotherapy with prophylactic para-aortic irradiation and concurrent chemotherapy are safe and well tolerated for patients with FIGO stage IIB-IIIB cervical carcinoma. The preliminary survival results were acceptable. Long-term follow-up is needed to evaluate the side effects and outcome with this intensive treatment combination.

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Key words: Cervical carcinoma, Prophylactic para-aortic irradiation, Concurrent chemotherapy, Toxicity.

INTRODUCTION

Incidences of para-aortic lymph node (PALN) metastasis in patients with carcinoma of the uterine cervix were reported to range from 6% to 25% in the Gynecology Oncology Group (GOG) study [2]. Several efforts have been made to eradicate the para-aortic disease by prophylactic irradiation, irradiation of known PALN metastasis at the time of initial diagnosis of cervical cancer, and irradiation for recurrent disease [7,8,16,20]. Of these, the best outcome was obtained with the use of prophylactic para-aortic treatment in the Radiation Therapy Oncology Group (RTOG) randomized trial [18]. Furthermore, the addition of chemotherapy to irradiation confers significant benefits in at least five randomized trials, in pre-operative, post-operative, and definitive settings [10,13-15,18]. One of these studies even demonstrated superior results in survival and local/distant disease control with pelvic radiotherapy and chemotherapy than with pelvic and para-aortic radiotherapy alone [13]. Several treatment-related side effects deserved special attention with either para-aortic irradiation or concomitant chemotherapy [6,13,20]. However, few studies addressed the toxicity and outcome with prophylactic para-aortic irradiation and concomitant chemotherapy. In our institution, we designed a phase I/II trial with prophylactic para-aortic radiotherapy and concurrent chemotherapy for patients with stage IIB-IIIB cervical carcinoma. We reported the preliminary outcome and treatment-related toxicities in the interim analysis.

MATERIALS AND METHODS

From June 1998 through June 2001, 20 patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIB or IIIB primary cervical carcinoma were treated at Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan. Fifteen patients were staged as IIB and 5 patients as IIIB. Patients' age ranged from 31 to 69, with a mean of 50. Pathological examinations of biopsy of the cervical tumor were obtained for all patients. Histological features were squamous cell carcinoma in 18 patients and adenocarcinoma in 2. The initial evaluation included chest radiography, abdominal sonography, cystoscopy, proctoscopy, computed tomography (CT) or magnetic resonance images (MRI) of pelvis and low abdomen, a complete blood count, and blood chemistries of liver and renal functions. No patient had enlarged lymph node at the para-aortic area in the initial work-up.

All patients were treated with definitive concomitant radiotherapy and chemotherapy. Radiation treatment was given to the pelvis and prophylactically to the para-aortic area. External-beam radiation was delivered with four-field (anteroposterior, posteroanterior, and the two lateral opposed fields) technique, using 18-MV photons. The pelvis and para-aortic

areas were treated in a continuous field, with a superior border at the space between L1 and L2 and an inferior border at the mid-pubis or 3-4 cm below the most distal vaginal or cervical site of disease. A 1.5-2 cm margin was designed lateral to the pelvic bone rim to treat pelvic lymph nodes. Lateral fields were designed to encompass S3 posteriorly, with a margin of at least 3 cm from the primary cervical tumor. Multi-leaf collimator was used to shape the radiation fields. The radiation dose was keyed to the isocenter of the beams. The total dose to the para-aortic area was 45 Gy and to the whole pelvis was 50.4 Gy, given at a daily fraction of 1.8 Gy. A midline shielding with rectangular block was used after 41.4 Gy or 45 Gy. Area of parametrial disease was irradiated with an additional boost of 9 Gy in 5 fractions.

Intracavitary brachytherapy with high-dose-rate Iridium-192 was given after the midline block was used. A dose of 4-7 Gy per fraction was delivered to point A, based on the dose limit of rectum and bladder derived from the simulated computer treatment plan. Patients were treated once or twice a week, with a total of four to five insertions and point A dose of 22-30 Gy. The goal total dose to point A was 80-85 Gy and 85-90 Gy of low-dose-rate equivalent dose for patients with stage IIB and IIIB, respectively. The dose constraints were 75 Gy for rectum and 80 Gy for bladder.

Chemotherapy included 2 concurrent cycles of cisplatinum during radiotherapy and 2 cycles of cisplatinum and 5-fluorouracil after completion of radiation treatment. Concomitant chemotherapy with an intravenous infusion of cisplatinum 60-80 mg/m^2 was given on day 1 and day 29. Post-radiation chemotherapy consisted of an intravenous infusion of cisplatinum 60-80 mg/m^2 over a four-hour period followed by 5-fluorouracil 600-800 mg/m^2 over a 120-hour period, at one and two months after completion of radiotherapy.

Patients were evaluated weekly by clinical assessments, a complete blood count, and a pelvic examination. Blood chemistries were ordered on a needed basis. Patients had a pelvic examination and the placement of brachytherapy apparatus under anesthesia at the time of each intracavitary treatment. After completion of chemoirradiation, patients were followed every three months for the first three years, and every six months during the fourth and fifth years. The evaluation consisted of physical examination, pelvic examination, and Pap smear on a 3-month interval, chest radiography and abdominal sonography on a 6-month basis, and CT or MRI of pelvis annually. Toxicity was assessed at the time of each evaluation with the use of Acute and Late Radiation Scoring Scheme of the RTOG. Survival outcome was calculated by Kaplan-Meier method.

RESULTS

The median follow-up interval was 15 months, with a range of 4 to 38 months. All patients completed the planned pelvic and para-aortic irradiation. The median total duration of radiation was 61 days, ranged from 53 to 81 days. The dose of external-beam radiotherapy was homogeneous in all patients, with 45 Gy to the para-aortic area, 50.4 Gy to the pelvis, 59.4 Gy to the parametrial disease, except one patient with 66.4 Gy to the gross pelvic nodes by conformal design. All patients had the planned courses of the intracavitary brachytherapy. The average dose to point A was 25.4 Gy from the intracavitary brachytherapy, ranged from 22.2 to 29.6 Gy. All 20 patients (100%) completed 2 cycles of concurrent chemotherapy during radiotherapy. Sixteen patients (80%) had 2 cycles of post-radiation chemotherapy. Post-radiation chemotherapy was discontinued or modified because of prolonged recovery from hematological toxicity, diminished performance status, or refusal. The details of chemotherapy compliance were listed in Table 1.

Table 1. Compliance of chemotherapy for patients with cervical cancer

Cycles of chemotherapy	Number	Percent
Concurrent chemotherapy		
2	20	100
Post-radiation chemotherapy		
0	3	15
1	1	5
2	16	80
Reasons for non-compliance or modification of chemotherapy		
Prolonged hematological toxicity	3	15
Diminished performance status	3	15
Refusal	2	10

At the time of last follow-up, all patients were alive and the 2-year survival rate was 100%. One patient had isolated local recurrence at 19 months after the diagnosis of stage IIB disease, with the 2-year local control rate of 83%. This patient was successfully salvaged with exenteration and still remained alive and disease-free. One patient developed isolated lung metastasis at 10 months after the diagnosis of stage IIB disease and is still receiving salvage chemotherapy. The 2-year distant metastasis-free survival was 93%. No patient had PALN metastasis (Fig 1).

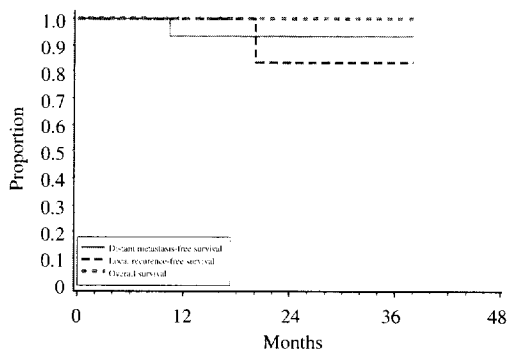

Figure 1. Survival outcomes for the 20 patients with cervical cancer

All acute treatment-related toxicities were mild to moderate, reversible and tolerable. No patient had grade IV acute toxicity. Most of them were hematological and gastrointestinal side effects. For gastrointestinal toxicity, there were four patients (20%) with grade III reaction. For hematological toxicity of leukopenia, there were five patients (25%) with grade III reaction. All others had the toxicities classified as grade 0 to II. No patient had the interruption of radiation therapy due to the treatment-related adverse effects. Until last follow-up, most late toxicities were the injuries to the bowels. Two patients had radiation injury of small intestine requiring surgery (grade III), with one of them also had grade III radiation colitis. One of the 2 patients received 66.4 Gy of external-beam radiotherapy to the pelvic lymphadenopathies and had clinical evident radiation-related bowel obstruction, radiation colitis, and sacral plexopathy. The second patient was treated with 59.4 Gy to the pelvic lymphadenopathies and had bowel obstruction and the fistula between bowels and urinary bladder. The treatment-related toxicities were shown in Table 2.

DISCUSSION

The incidence of PALN metastasis in patients with cervical cancer usually correlates with clinical tumor stage. In the GOG study of surgical staging for patients with carcinoma of the uterine cervix, the incidences of positive para-aortic nodes were 6%, 16%, and 25% for stage I, II, and III, respectively [2]. Fine et al. reported a much higher rate of PALN metastasis from the retroperitoneal or transperitoneal pretherapy surgical staging, with 23.6% for

Table 2. Treatment-related toxicities for the 20 patients with cervical cancer

Number	Grade 0	Grade I	Grade II	Grade III	Grade IV
Acute side effects					
Upper gastrointestinal tract	2	8	6	4	0
Lower gastrointestinal tract	0	2	17	1	0
Hepatic system	12	8	0	0	0
Genitourinary system	11	6	2	1	0
Hemoglobin	2	11	5	2	0
Leukocytes	0	4	11	5	0
Platelets	13	5	1	1	0
Chronic side effects					
Stomach/duodenum	18	1	1	0	0
Small bowels	17	1	0	2	0
Large bowels	14	4	1	1	0
Urinary bladder	19	0	0	1	0
Sacral plexopathy	19	0	0	1	0

stage II and 37.6% for stage III disease [5]. The hypothesis has been generated with some of the disease progression of cervical carcinoma through regional pelvic lymphatics to the PALN prior to systemic dissemination [17]. Such a significant histological evidence of para-aortic nodal metastasis and the possible spreading manner aroused special attention and initiated further study of prophylactic para-aortic irradiation. RTOG began the randomized trial of prophylactic para-aortic irradiation for patients with bulky IB/IIA and IIB cervical cancer in 1979 [16,18]. The ten-year results revealed the survival gain of 11% with this treatment design. More important is that the superior survival was likely from the reduction of distant metastasis in the para-aortic irradiation arm. It supported to some extent that prophylactic para-aortic irradiation prevented some systemic metastasis via the indolent micrometastasis in the PALN.

On the other hand, a subsequent RTOG randomized study starting 1990 investigated the difference in disease control and survival between pelvic/para-aortic irradiation and pelvic radiotherapy with concurrent chemotherapy [13]. Surprisingly the chemoirradiation group had better survival, local control, and reduction of distant metastasis. However, this trial enrolled patients with stage IB/IIA of tumor diameter more than 5 cm, and all stage IIB-IVA [13], which was different from the inclusion criteria of bulky IB/IIA and IIB in RTOG 79-20 trial [16,18]. In the subgroup analysis the survival benefit was evident only in patients with stage IB-IIB disease. Concurrent chemotherapy did not significantly improve survival for those with stage III/IVA tumors. Similarly, another randomized trial of prophylactic para-aortic irradiation in the EORTC radiotherapy group recruiting stage III patients also showed negative results in survival [9]. Therefore, it is possible that the survival impact of prophylactic para-aortic irradiation was insignificant for patients with more advanced disease extent beyond early stage.

The prognosis has been dismal for patients with synchronous occurrence or recurrence of cervical cancer at the para-aortic area. Grigsby et al. reported a 5-year survival rate of 32% for patients having biopsy-proven positive PALN treated with definitive radiation therapy [7]. Seventeen of the 20 patients with recurrence in their study had distant metastasis as part or sole of disease recurrence after radiotherapy. Stryker et al. demonstrated a 5-year survival rate of 29% for patients treated with extended-field radiotherapy for para-aortic lymph node metastasis [19]. They found the 15% survival differ-

ence for those with microscopic and gross PALN metastasis. Vigliotti et al. published a comprehensive report indicating the prognostic factors for patients with PALN metastasis [21]. Patients who benefit most from extended field irradiation are those in whom the residual disease in the para-aortic area measures less than 2 cm in size, whose disease extends no higher than L3, and whose pelvic disease can be controlled effectively. Cunningham et al. indicated the best outcome for patients with early-stage cervical cancer but surgically proven para-aortic nodal metastasis, treated with extended field irradiation [3]. However, the major morbidity rate was as high as 19%. Some series tried to use the altered fractionation of radiotherapy to improve the control rate and to reduce the treatment-related morbidity [6,12]. However, the benefits of disease control were limited and the adverse effects were beyond the usual tolerance. Not surprisingly, the recurrence of para-aortic nodes is frequently associated with severe clinical problems. Grigsby et al. reported the triad of leg edema, hydronephrosis, and sciatic pain that might result in disastrous quality of life and difficulties in aggressive treatment integration [8].

With the recent evidences of survival gain by the use of prophylactic para-aortic irradiation [18] and concomitant chemotherapy [10,13-15,22], we designed the phase I/II study of the combined modalities for patients with FIGO stage IIB-IIIB cervical carcinoma. The documented benefit of prophylactic para-aortic irradiation was for patients with FIGO stage IB2/bulky IIA, and IIB tumors [18], while that of concurrent chemotherapy with cisplatinum and 5-fluorouracil was for patients with locally advanced disease [13,15]. It is our hope that the simultaneous use of prophylactic para-aortic irradiation and concurrent chemotherapy is beneficial in the reduction of systemic metastasis and in the improvement of local control. Currently there has not been the report using chemotherapy concurrently with irradiation to the para-aortic area in prophylactic setting, except for those in definitive setting for the proven para-aortic metastasis. To avoid excessive bowel irritation and bone marrow suppression, we used the single agent of cisplatinum of moderate dose concomitantly with pelvic and para-aortic irradiation. The supplement cycles of chemotherapy with cisplatinum and 5-fluorouracil after completion of radiotherapy were designed to obtain the possible effect of systemic control. Total treatment time of radiotherapy plays an important role in disease control and survival for patients with cervical cancer [4,11]. The design was based on the integration of both modalities with no delay or interruption of radiotherapy due to treatment-related adverse effects. In our preliminary analysis all patients completed the radiation therapy with no interruption or unacceptable side effects.

Most of the treatment-related toxicities were mild to moderate in the series using pelvic and para-aortic irradiation with or without concurrent chemotherapy. In GOG 125 study extended field radiotherapy (45 Gy) and concurrent chemotherapy with cisplatinum and 5-fluorouracil were given to patients with documented PALN metastasis. They reported 15.1% patients with grade 3 or 4 acute hematological toxicity and 18.6% of patients with grade 3 or 4 acute gastrointestinal toxicity [20]. Our data demonstrated 25% and 20% of patients with hematological and gastrointestinal toxicities, respectively. In contrast, the side effects were less toxic in the series with pelvic and para-aortic irradiation alone. Grigsby et al. reported well tolerance to acute reactions and few late toxicities for patients with positive PALN metastasis treated with 30.6-55 Gy of para-aortic irradiation [7]. RTOG randomized trial designed the radiotherapy arm with 45 Gy to the para-aortic area [13]. It showed 3% and 2% of patients with equal to or more than grade 3 acute hematological and the other toxicities, respectively.

Although the follow-up interval was too

short to conclude the definite disease control, the treatment-related toxicities were moderate and tolerable. The acute and chronic side effects were similar to those reported in the other series [1,13,15,18]. Most of them were gastrointestinal or hematological and self-limited. There were only one patient with local recurrence, another patient with distant metastasis, and no recurrence at the para-aortic area. The preliminary results were promising and encouraging, but needed to be conservatory for their limited follow-up period. It deserves further attention to have long-term follow-up and enrollment of more patients in this study.

In conclusion, definitive radiotherapy with prophylactic para-aortic irradiation and concurrent chemotherapy are feasible and well tolerated with moderate toxicities for patients with FIGO stage IIB-IIIB cervical carcinoma. The preliminary results in survival and disease control were acceptable. Long-term follow-up is demanded to evaluate the side effects and outcome with this intensive combined modalities of treatment.

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子宮頸癌病人的預防性主動脈旁淋巴區放射治療與合併化學治療：初期成果與副作用分析

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目的：本研究目的在分析第二期 B 與第三期 B 子宮頸癌病人接受全程放射治療中，加入預防性主動脈旁淋巴區照射與合併化學治療的初期存活成果與治療相關副作用分析。

材料與方法：1998 年 6 月至 2001 年 6 月間，20 位第二期 B 或第三期 B 子宮頸癌且無主動脈旁淋巴腺轉移的病人，被納入本研究分析中。治療組合包括全程骨盆腔放射治療，預防性主動脈旁淋巴區放射治療，合併放射治療療程中的化學治療，與放射治療療程結束後的化學治療。放射治療設計有 45 Gy / 25 次的主動派旁淋巴區體外放射治療，50.4 Gy / 28 次的骨盆腔體外放射治療，9 Gy / 5 次的子宮頸旁軟組織加強體外放射治療，以及 Point A 4-5 次共計 22-30 Gy 的體腔內近接放射治療。化學治療包括放射療程中第 1 及 29 天共兩次的 cisplatinum 60-80 mg/m^2，以及放射療程後 1 及 2 個月的 cisplatinum 60-80 mg/m^2 和連續注射 5 日的 5-fluorouracil 600-800 mg/m^2，病人治療結束後定期返回門診追蹤檢查。存活成果分析以 Kaplan-Meier 方法分析，治療相關副作用以 RTOG 標準評定，中位數追蹤時間為 15 個月。

結果：所有病人皆完成原定的放射治療及放射療程中的兩次合併化學治療，16 位病人（80%）另完成了放射療程後的兩次化學治療，其中 4 位病人在化學治療藥物上有所調整。1 位病人追蹤時出現局部復發，2 年局部控制率為 83%，另一位病人出現肺部轉移，沒有病人出現主動脈旁淋巴復發，所有病人均仍存活，2 年存活率為 100%。所有病人皆沒有第四度的急性副作用，大多數的治療相關副作用為腸胃道及血液系統的反應，四位病人（20%）出現第 3 度腸胃道副作用，五位病人（25%）出現第 3 度血液系統副作用，僅有 2 位病人出現超過 2 度以上的長期併發症。沒有病人因為治療副作用而造成放射治療療程延誤或中斷。

結論：全程放射治療中加入預防性主動脈旁淋巴區放射治療及合併化學治療，對第二期 B 及第三期 B 的子宮頸癌病人是安全且可忍受的治療方式。初期存活成果是足以接受的，本研究需要更長時間的追蹤，以確認這種強度的組合治療方式的控制成效和治療副作用。

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關鍵詞：子宮頸癌、預防性主動脈旁淋巴區放射治療、同步化學治療、治療毒性