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Use of Cisplatin and 5-Fluorouracil-based Chemotherapy and Radiotherapy after Radical Surgery in High Risk Early Stage Cancer of the Cervix

Su Seong Soon [a], Yin Nin Chia [b], Kwai Lam Yam [c], Eng Hseon Tay [d]

ABSTRACT

Objectives: To determine whether the use of combined cisplatin and 5-fluorouracil chemotherapy with radiotherapy (CCRT) after radical hysterectomy improves the recurrence and survival of high-risk early stage cervical cancer patients.

Methods: From January 1997 to October 2007, case records of 340 women who had undergone radical hysterectomy and bilateral pelvic lymphadenectomy for early cervical cancer at KK Women's and Children's Hospital were reviewed. 82 patients with high-risk factors such as parametrial, lymph node or surgical margins involvement on histology were included in the study. Adjuvant CCRT were given to 68 patients, consisting of cisplatin ($70mg/m^2$ on day 1) and 5-fluorouracil ($1gm/m^2$ from day2 to day5) for 4 cycles every 3 weeks beginning 2-4 weeks after surgery. Radiotherapy was started concurrently with the first cycle of chemotherapy. 24 patients who did not receive CCRT or received radiotherapy only (control group) were included into the study for comparison purposes. Data regarding recurrence pattern and survival were analyzed.

Results: The median follow-up period was 30 months. 5 patients (20.8%) in the control group and 15 patients (25.7%) in the CCRT group had disease recurrence. The 5-year progression-free survival is 83.3% in the control group and 74.5% in the CCRT group. The 5-year overall survival is 83.3% in the control group and 78.2% in the CCRT group.

Conclusions: Use of CCRT did not improve the survival outcomes in cervical cancer patients with high-risk factors.

Keywords: cervical cancer, cisplatin, 5-fluorouracil, radiotherapy

INTRODUCTION

Worldwide, cervical cancer is the seventh most common cancer, and the third most common cancer in women, in which it comprises 9.8% of all cancers or 371,200 new cases a year [1]. Cervical cancer is responsible for 190,000 deaths annually [2]. About 78% of these deaths occur in developing countries, where it is the leading cause of cancer mortality for sub-Saharan Africa, tropical South America, Caribbean, South-central Asia and Pacific Island Nations [2]. For women with early stage disease, both radical hysterectomy with pelvic lymphadenectomy and radiation therapy can be used as primary therapy. The 5-year survival rate is similar for both methods of treatment, quoted at 83% in a study [3]. Radical surgery is generally preferable for younger women with early stage disease (stages 1A2, 1B and IIA cervical cancer) as it offers better preservation of sexual and gonadal function, and avoidance of late effects of radiation therapy. It also allows assessment of the lymph node status, which is strongly associated with prognosis and survival, and the possible utilization of radiotherapy for pelvic relapses.

Certain risk factors for cervical cancer recurrence have

[a, b, c, d] *Gynaecological Oncology Unit (GOU), KK Women's and Children's Hospital, 100, Bukit Timah Road, Singapore 229899*

[a] *corresponding author. Fax: (65) 62918135*
Email address: soonsuseong@gmail.com

been identified. Various studies have reported that large tumor diameter, deep stromal invasion, grade of tumor and positive lympho-vascular space involvement increases the risk of tumor recurrence [4,5,7]. Close vaginal margins and parametrial extension of tumor are also important predictors of patients' survival [6,7,8]. Among all these variables, pelvic lymph node status has been identified as an independent and significant prognostic factor; the 3-year disease free interval drops from 85.6-87% to 61-74.4% in the presence of positive pelvic nodes [5,8,9].

Adjuvant therapy utilizing radiation, chemotherapy or both have been used to reduce the risk of relapse in patients with these risk factors. A landmark Gynecologic Oncology Group (GOG) study has concluded that adjuvant pelvic radiotherapy following radical surgery reduces the number of recurrences in women with stage 1B cervical cancer with risk factors such as more than 1/3 stromal invasion, capillary lymphatic space involvement and large tumour diameter [10].

Another landmark study, also known as GOG protocol #109, concentrated on three other adverse prognostic factors (positive pelvic lymph nodes, positive margins or positive parametrium) and compared the addition of cisplatin-based chemotherapy to pelvic radiation for patients with these factors, who had undergone radical hysterectomy and pelvic lymphadenectomy for cervical cancer[11]. The addition of cisplatin-based chemotherapy to radiation therapy improves the 4-year progression-free and overall survival for these patients from 63% and 71%, to 80% and 81%, respectively. KK Women's and Children's Hospital (KKH) in Singapore has utilized this treatment regime, which combines cisplatin and 5-fluorouracil (FU) with radiotherapy (CCRT) since 1999. We attempt to assess our experience with this treatment regime in this observational study.

MATERIALS AND METHODS

This was a 10 year retrospective study was conducted from a period of 10 years and 10 months from January 1997 to October 2007. CCRT was first offered to patients at KKH in June 1999 and was routinely offered to all high-risk patients since 2000. We included a group of patients who was not offered this regime, who either did not receive any adjuvant treatment or radiotherapy alone (non-CCRT Group), into our study for comparison purposes.

The case records from all patients who had undergone Piver class III radical hysterectomy and bilateral pelvic lymphadenectomy during that period were reviewed. Patients who received or were qualified to receive adjuvant concurrent chemoradiotherapy, based on the GOG #109 protocol, were included into the study. Demographic data such as patients' age at diagnosis, ethnicity and ECOG (Eastern Cooperative Oncology Group) status were recorded. Information regarding the disease (tumor size, histological type, grade and prognostic factors such as lymph node, parametrial and margin involvement) was obtained from the formal staging forms and histopathological report. Decisions for adjuvant therapy were made at the tumor board meetings, which were formally documented and filed. All information regarding adjuvant therapy (radiotherapy, chemotherapy or both) was obtained.

For patients receiving CCRT, the first cycle of chemotherapy was usually initiated within 6 weeks following surgery. Hickman's central venous line was inserted prior to the start of the first cycle of chemotherapy. A total of 4 cycles of chemotherapy with 3 weekly intervals was planned, with each cycle consisted of cisplatin (70mg/m^2) on day 1 of cycle followed by 5-fluorouracil infusion (4g/m^2 total dose), from days 2 to day 5. Radiotherapy is started together with the first cycle of chemotherapy. The treatment was administered at the National Cancer Centre, Singapore. The external beam pelvic radiotherapy was given over a period of about 5 weeks, using a 3-field or 4-field technique, utilizing a total dose of 45-50.4Gy in 25-28 fractions over a period of about 5 weeks. Vaginal vault brachytherapy was given after pelvic radiotherapy, prescribed to 0.5cm from the surface of the vaginal cylindrical applicator using a high dose rate technique. All information regarding side effects were assessed and analyzed according to the GOG toxicity criteria.

Upon completion of treatment, patients were given follow-up appointments at the gynecological cancer clinic, where they were assessed clinically for any evidence of recurrence. If recurrence was suspected, investigations such as blood tests, imaging and biopsies were taken to confirm recurrence. Cases with suspected recurrence were routinely discussed at the hospital's weekly tumor board meeting for joint decision regarding further investigations and management. The date and site of all recurrences and the date of death from the disease were recorded in patients who developed recurrence of disease. Data were analyzed using the SPSS package for Windows version 14.0. Statistical comparisons in different groups were done using two-sample Student's t test for continuous variables and chi-square test for categorical variables. Progression-free and overall survivals were calculated using the Kaplan-Meier method and compared by the log-rank test. The association of risk factors with survival was assessed using the log-rank test of survival equality. A two-sided p value of less than 0.05 was considered statistically significant.

Results

A total of 340 patients with early stage cervical cancer (from stages 1A2 to IIA) have undergone radical hysterectomy and bilateral pelvic lymphadenectomy at KKWCH from January 1997 to October 2007. After reviewing the case records of these 340 patients, 87 patients were noted to have at least one of the high-risk criteria for CCRT. Out of the 87 patients, 3 patients' case records were incompletely recorded, 1 patient had adenocarcinoma with papillary serous component of the cervix and had adjuvant concurrent chemoradiotherapy with paclitaxel and carboplatin, and 1 patient return to her home country for adjuvant therapy. These patients were not included in the study, leaving a total of 82 patients for analysis.

Out of the remaining 82 patients, 5 patients refused and did not receive any adjuvant radiotherapy or chemotherapy for personal reasons. Another 19 patients received only adjuvant radiotherapy but not chemotherapy; 9 patients were not offered and did not receive any adjuvant chemotherapy, 6 patients refused adjuvant chemotherapy alone but decided for adjuvant radiotherapy, 4 patients were not offered adjuvant chemotherapy (2 patients due to poor social support, 2 patients due to age and 1 patient due to hearing impairment). Thus, 58 patients (70.7%) were offered and underwent CCRT (CCRT group) and 14 patients (29.3%) either underwent radiotherapy alone or did not receive any adjuvant therapy (Non-CCRT group).

The minimum follow-up time was 1 month and maximum follow-up time was 10 years and 10 months. The median follow-up time was 30 months. 56 patients have complete 1 year, 44 patients have complete 2 years, 35 patients have complete 3 years, 31 patients have complete 4 years, 26 patients have complete 5 years and 2 patients have complete 10 years follow-up.

The patients' characteristics are shown in Table 1 and include age, race, clinical stage, cell type, primary lesion size, and presence of positive margins, parametrial involvement and lymph node involvement. There were no significant differences between the 2 groups of patients.

Table 1. Patient Characteristics

Characteristics value	CCRT Group (n=58)	Non-CCRT Group (n=24)	*p*
Age			
Median	50	49.5	0.111
Range	31-68	29-77	
Race			
Chinese	48 (82.8%)	23 (95.8%)	0.432
Malay	6 (10.3%)	1 (4.2%)	
Indian	1 (1.7%)	0	
Others	3 (5.2%)	0	
ECOG status			
0	43 (74.1%)	18 (75%)	0.273
1	15 (25.9%)	5 (20.8%)	
2	0	1 (4.2%)	
Stage			
1B1	30 (51.7%)	18 (75%)	0.113
1B2	13 (22.4%)	4 (16.7%)	
IIA	15 (25.9%)	2 (8.3%)	
Cell Type			
Squamous	38 (65.5%)	14 (58.3%)	0.447
Adenocarcinoma	14 (24.1%)	5 (20.8%)	
Adenosquamous	6 (10.3%)	5 (20.8%)	
Lesion size (cm)			
Median	3.0	3.0	0.258
Range	1-8	1-5	
Positive Pelvic Nodes			
Yes	40 (69%)	15 (62.5%)	0.375
No	18 (31%)	9 (37.5%)	
Positive Margins			
Yes	8 (13.8%)	1 (4.2%)	0.271
No	29 (82.9%)	13 (92.9%)	
Parametrial Involvement			
Yes	29 (50%)	14 (58.3%)	0.628
No	29 (50%)	10 (41.7%)	

A total of 77 patients underwent adjuvant radiotherapy (58 patients from CCRT group and 19 patients from Non-CCRT group) as 5 patients (6.1%) refused CCRT. 3 patients (5.2%) from the CCRT group had delayed in the completion of radiotherapy; 2 patients (2.6%) required prolonged post-operative bladder training, 1 patient had febrile neutropenia. The delays ranged from 1-3 weeks. 1 patient (1.3%) died while undergoing CCRT; she was undergoing radiotherapy and had 2 cycles of chemotherapy when she was admitted to another hospital where she passed away at the emergency department.

Out of these 58 patients in the CCRT group, 7 patients (12.1%) did not completed the 4 courses that they are scheduled to receive. 4 patients (6.8%) had only 2 courses and 3 patients (5.1%) had only 3 courses of chemotherapy. 3 patients (5.1%) were not keen to continue the treatment due to personal reasons, 2 patients (3.4%) had their chemotherapy cancelled due to grade 4 thrombocytopenia and neutropenia, 1 patient (1.7%) died during the treatment and 1 patient (1.7%) developed progressive disease with bony metastases during the course of her treatment and her chemotherapy regime was changed.

Out of the 51 patients who completed all 4 courses of chemotherapy, 17 patients had some delay in completion. The mean delay is 2 weeks (range 1 to 8 weeks) and the reasons include severe neutropenia(55%), fever/sepsis(10%), diarrhea and vomiting (25%), patients' wishes (5%) and impaired renal function (5%).

Out of the 58 patients who had CCRT, 27 patients (46.6%) have suffered grade 3 or 4 toxicity due to adjuvant therapy (see Table 2). Most grade 3 or 4 toxicities were gastro-intestinal and hematologic toxicities. 1 patient has the cisplatin alone without FU due to grade 4 neutropenia. 1 patient passed away while undergoing CCRT, as mentioned earlier. It remained unconfirmed if the death was treatment-related but she suffered from grade 3 anaemia and neutropenia during CCRT, which required admission, blood transfusion and granulocyte-colony stimulating factor injections.

Table 2. Grade 3 or 4 Toxicity for patients who received CCRT (n=58)

Toxicity	No	%
Diarrhea	5	8.6
Vomiting	4	6.9
Neutropaenia	6	10.3
Febrile neutropaenia	4	6.9
Anemia	1	1.7
Neurotoxicity	3	5.1
Ototoxicity	1	1.7
Lymphoedema	3	5.1

Note: Some patients have more than one grade 3 or 4 toxicity

Survival analysis

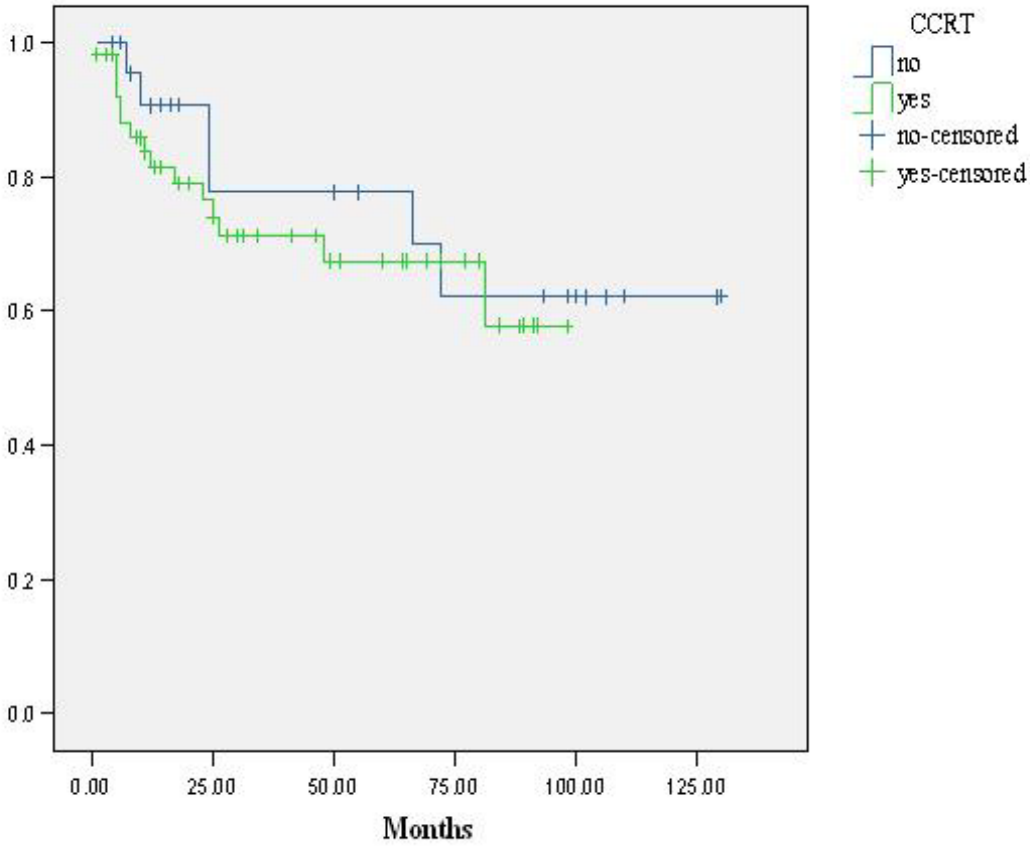
Out of the 82 patients in this study, 1 patient had persistent disease during treatment. She was undergoing CCRT and had completed 2 cycles of chemotherapy when she was noted to have bony (lumbar and thoracic vertebrae, and left trochanter of femur). The radiation field was adjusted to include the hip and the spine but the patient developed malignant ascites with intestinal obstruction and died 19 months later. 1 patient died during her treatment with CCRT, as mentioned earlier. 1 patient died from advanced cancer of stomach 4 years after she completed CCRT. As her cervical cancer (squamous cell) was confirmed to be histologically different from the adenocarcinoma of the stomach, this patient was not included in the analysis for overall survival These 3 patients were not included in assessment of survival, leaving 79 patients (55 who received CCRT and 24 who did not) for analysis of recurrence of disease.

A total of 20 patients (24.4%) had recurrence of disease (Table 3), 27.3% from the CCRT group and 21% from the Non-CCRT group. 6 patients (7.3%) had local recurrence and 14 patients (17.1%) had distant recurrence, with para-aortic nodes the commonest site of recurrence (9.7%).

Table 3. Site of first recurrence

Site of first recurrence	Non-CCRT group (n=24)	CCRT group (n=55)
Local		
Vault		1(1.8%)
Pelvis	1(4.2%)	1(1.8%)
Vault and pelvis	2(8.4%)	1(1.8%)
Distant		
Para-aortic		3(5.4%)
Abdomen and lung	1(4.2%)	1(1.8%)
Lung and para-aortic	1(4.2%)	1(1.8%)
Bone and para-aortic		1(1.8%)
Liver and para-aortic		2(3.6%)
Bone		3(5.4%)
Lung		1(1.8%)

Figure 1
Progression-free survival for patients who received and did not receive CCRT



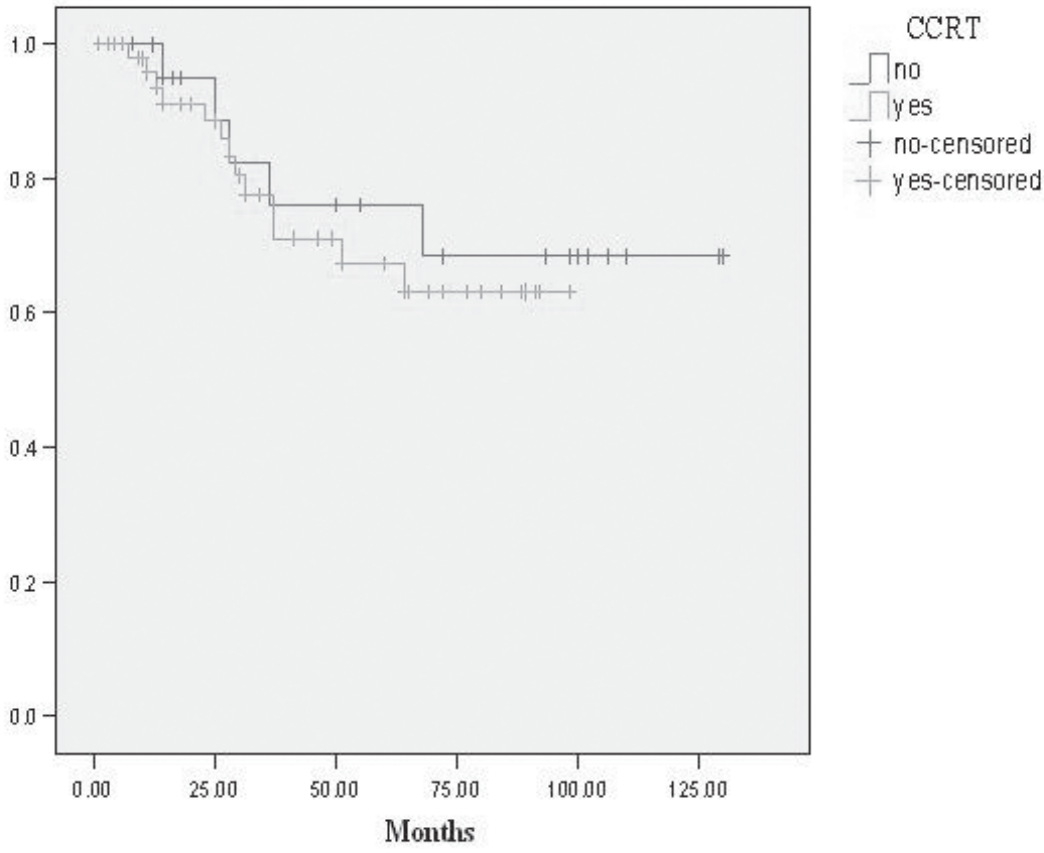
Comparison of the Kaplan-Meier progression-free survival curves for patients scheduled to receive CCRT and patients who were not. The difference in progression-free survival between the group of patients who received and did not receive CCRT is not significant (p= 0.537).

Comparison of the Kaplan-Meier overall survival curves for patients scheduled to receive CCRT and patients who were not. The difference in overall survival between the group of patients who received and did not receive CCRT is not significant (p= 0.617).

The 5-year progression-free survival is 83.3% in the control group and 74.5% in the CCRT group. The 5-year overall survival is 83.3% in the control group and 78.2% in the CCRT group.

Figure 2

Overall survival for patients who received and did not receive CCRT



DISCUSSION

Use of radiotherapy post-operatively after surgery for high-risk, stage 1B lymph node negative cervical cancer was shown to be beneficial in reducing the risk of recurrence by various studies [10,2,13]. However, these studies did not involve patients with positive pelvic lymph nodes, which is shown to be a far more significant prognostic factor [5,8,9]. GOG protocol #109 regime for high-risk post-operative patients, which included those with positive pelvic lymph nodes, was addressed by William A. Peters III et al in the 1999 GOG study [11] and the findings was further supported by another study by HS Ryu et al [14].

The concurrent use of chemotherapy with radiotherapy has gained worldwide attention in the recent years. Agents that have been identified as radiosensitizers include fluoropyrimidine (fluorouracil and fluorodeoxyuridine), gemcitabine and the platinums [15]. Cisplatin has been extensively studied as one of the most active single agents in carcinoma of the cervix. The use of cisplatin with radiotherapy has many advantages; the two treatment act synergistically to increase the tumor cell kill by inhibiting the repair of radiation-induced damage, inducing tumor cells into a radiation sensitive phase of the cell cycle and reducing the fraction of hypoxic cells that are resistant to radiation. It is also possible that chemotherapy may increase cell kill by itself and reduce risk of distant or micrometastases, although the doses administered concurrently with radiation are far lower.

The use of concurrent cisplatin with radiotherapy was found to improve overall survival in women with locally advanced cervical cancer, large 1B tumors (prior to surgery) and high-risk early-stage disease (following surgery) [16,17,18].

Various studies have evaluated the combination of 5-fluorouracil and cisplatin with radiotherapy as part of cervical cancer treatment, with the belief that fluorouracil, as a potential radiosensitizer, can provide additional advantages as an anti-metabolite which inhibits cell synthesis and repair of radiation-induced cell damage. Most studies concentrate on the use of FU as a radiosensitiser for colonic malignancy [19,20]. For use in cervical cancer, the earlier studies focused mainly on the usage of FU and cisplatin in patients with locally advanced disease.

In a study by Morris et al, the addition of chemotherapy with cisplatin and FU to radiotherapy improved survival in women with locally advanced cervical cancer (stages 1B2 and IIA with at least 5cm tumors, IIB through IVA). 5-year progression-free and overall survival improved from 40% and 58% with radiotherapy alone, to 67% and 73% with combination therapy [21]. This finding was also reflected in another study, which compared cisplatin and FU with extended field radiotherapy for women with locoregionally advance disease [22].

Rose et al compared radiotherapy with 3 concurent chemotherapy regimens (cisplatin alone, cisplatin, fluorouracil and hydroxyurea; and hydroxyurea alone) in patients with locally advanced cervical cancer stages IIB to IV. Use of cisplatin alone or in combination with other chemotherapy agents improved 24-months progression-free survival (64-67% versus 47%) when compared to use of hydroxyurea alone [23]. Another study also demonstrated that combination of cisplatin and FU offered better progression free and overall survival than hydroxyurea, when combined with radiotherapy for locally advanced cervical cancer (stages IIB-IVA) [24].

Our study demonstrated that no significant difference in both progression-free and overall survival between patients who received and did not receive CCRT. This significance of this finding is unclear due to the small numbers involved in this study. With as many as 17.2% of patients who did not complete or had delay in adjuvant therapy, this may have a significant effect on the risk of recurrence. The commonest risk factor present in the study group was pelvic nodal involvement. This may have contributed to para-aortic nodes being the commonest site of recurrence, as a result of lymphatic spread. Para-aortic nodal involvement affected almost 50% of the patients with recurrence (7 out of 15 patients) despite having chemotherapy. The addition of chemotherapy might not be as effective in reducing distant metastases as was suggested in many articles.

Hematological and gastrointestinal side effects are relatively common and this is consistent in other studies as well [11,14]. With the possibility of 1 case of treatment-related death, prompt assessment and treatment of moderate-to-severe toxicities is vital to prevent death, when these side effects should be manageable. Patient education regarding seeking immediate medical care is equally crucial.

As there appears to be lack of any significant benefits from cisplatin-FU combined chemoradiotherapy in terms of progression-free or overall survival in patients with high-risk cervical carcinoma in this study, re-consideration towards its use should be given. A possible alternative is the use of single agent cisplatin with radiotherapy. This may allow similar benefits in terms of reduction in recurrence and improvement in survival, and avoid the additional side effects associated with use of FU. After all, studies have consistently produced evidence supporting the use of cisplatin with radiotherapy [16,17,18,21,23,24]. Alternatively, consideration towards the use of combined cisplatin and FU being restricted to patients with tumor size of more than 2 cm or patients with more than one positive pelvic lymph node should be given, as is recommended in a re-analysis of the data from GOG protocol #109 [25].

REFERENCES

1. *Parkin DM, Pisani P, Ferlay J. Estimates of worldwide incidence from 25 major cancers in 1990. Int J Cancer 1999; 80: 827-841.*

2. *Pisani P, Parkin DM, Bray F and Ferlay J. Estimates of worldwide mortality from 25 cancers in 1990. Int J Cancer 1999; 83: 18-29.*

3. *Landoni F, Maneo A, Colombo A et al. Randomised study of radical surgery versus radiotherapy for stages 1B-IIA cervical cancer. Lancet 1997; 350: 535-540.*

4. *Delgado G, Bundy B, Zaino R, Sevin BU, Creasman WT, Major F. Prospective surgical pathological study of disease-free interval in patients with stage 1B squamous cell carcinoma of the cervix: A Gynecologic Oncology Group Study. Gynecol Oncol 1990; 38(3): 352-357.*

5. *Kristensen GB, Abeler VM, Risberg B, Trop C, Bryne M. Tumour size, depth of invasion and grading of the invasive tumor front are the main prognostic factors in early squamous cell cervical carcinoma. Gynecol Oncol 1999; 74(2): 245-254.*

6. *Estape RE, Angioli R, Madrigal M et al. Close vaginal margins as a prognostic factor after radical hysterectomy. Gynecol Oncol 1998; 68(3): 229-232.*

7. *Inoue T, Okumura M. Prognostic significance of parametrial extension in patients with cervical carcinoma stages 1B, IIA and IIB: a study of 628 cases treated by radical hysterectomy and lymphadenectomy with and without post-operative radiation. Cancer 1984; 54(8): 1714-1719.*

8. *Tsai CS, Lai CH, Wang CC et al. The prognostic factors for patients with early cervical cancer treated by radical hysterectomy and postoperative radiotherapy. Gynecol Oncol 1999; 75(3): 328-333.*

9. *Kamura T, Tsukamoto N, Tsuruchi N et al. Multivariate analysis of the histopathologic prognostic factors of cervical cancer in patients undergoing radical hysterectomy. Cancer 1992; 69(1): 181-186.*

10. *Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage 1B carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group study. Gynecol Oncol 1999; 73(2): 177-183.*

11. *Peters III WA, Liu PY, Barrett II RJ et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000; 18(8): 1606-13.*

12. *Kridelka FJ, Berg DO, Neuman M et al. Adjuvant small field pelvic radiation for patients with high risk, stage 1B lymph node negative cervix carcinoma after radical hysterectomy and pelvic lymph node dissection. Cancer 1999; 86(10): 2059-2065.*

13. *MN Rushdan, EH Tay, HS Khoo-Tan et al. Tailoring the field and indication of adjuvant pelvic radiation for patients with FIGO stage 1B lymph-nodes negative cervical carcinoma following radical surgery based on GOG score- a pilot study. Ann Acad Med Singapore 2004; 33: 476-72.*

14. *Ryu HS, Chun M, Chang KH, Chang HJ, Lee JP. Postoperative adjuvant concurrent chemoradiotherapy improves survival rates for high-risk, early stage cervical cancer patients. Gynecol Oncol 2005; 96(2): 490-495.*

15. *Lawrence TS, Blackstock AW, McGinn C. The mechanism of action of radiosensitization of conventional chemotherapeutic agents. Seminars in Radiation Oncology 2003; 13(1): 13-21.*

16. *Lukka H, Hirte H, Fyles A et al. Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer – a meta-analysis. Clin Oncol 2002; 14(3): 203-212.*

17. *Stehman FB, Ali S, Keys HM et al. Radiation therapy with or without weekly cisplatin for bulky stage 1B cervical carcinoma: follow-up of a Gynecologic Oncology Group trial. Am J Obstet Gynecol 2007; 197(5): 503.e1-e6*

18. *Keys HM, Bundy BN, Stehman FB et al. Cisplatin, radiation and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage 1B cervical cancer. N Engl J Med 1999; 340(15): 1154-1161.*

19. *Buchholz DJ, Lepek K, Rich TA, Murray D. 5-Fluorouracil-radiation interactions in human colon adenocarcinoma cells. Int J Radiation Oncol Biol Phys 1995; 32(4): 1053-1058.*

20. *Ojima E, Inoue Y, Watanabe H et al. The optimal schedule for 5-fluorouracil radiosensitization in colon cancer cell lines. Oncology Reports 2006; 16(5): 1085-1091.*

21. *Morris M, Eifel PJ, Lu J et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 1999; 340(15): 1137-1143.*

22. *Eifel P, Winter K, Morris M et al. Pelvic Irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high risk cervical cancer: an update of radiation therapy oncology trial (RTOG) 90-01. J Clin Oncol 2004; 22(5): 872-880.*

23. *Rose PG, Bundy BN, Watkins EB et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999; 340(15): 1144-1153.*

24. *Whitney CW, Sause W, Bundy BN et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjuvant to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol 1999; 17(5): 1339-1348.*

25. *Monk BJ, Wang J, Im S et al. Rethinking the use of radiation and chemotherapy after radical hysterectomy: a clinical-pathologic analysis of a Gynecologic Oncology Group/Southwest Oncology Group/Radiation Therapy Oncology Group trial. Gynecol Oncol 2005; 96: 721-728.*