นิพนธ์ต้นฉบับ

Phase III study of radiotherapy alone versus combination of mitomycin-C and 5-FU plus radiation in locally advanced cervical cancer : Preliminary results.

Prasert Lertsanguansinchai * Suree Thitathan *
Prayuth Rojpornpradit * Prabhatsorn Rajatapiti *

Lertsanguansinchai P, Thitathan S, Rojpornpradit P, Rajatapiti P. Phase III study of radiotherapy alone versus combination of mitomycin-C and 5-FU plus radiation in locally advanced cervical cancer : Preliminary results. Chula Med J 1993 Jul; 37(7) : 461-468

Between November 1988 and September 1990, 52 cases of advanced stage IIB and IIIB cancer of the uterine cervix at the Radiotherapy Unit, Department of Radiology, Chulalongkorn University Hospital were divided into 2 treatment groups; 25 patients were treated by conventional irradiation alone; while another 27 patients were treated by combination of mitomycin-C and 5-FU concomittently with conventional irradiation. There were no obvious benefits in locoregional control, but there were decreased in distant metastases in the chemotherapy arm. Median disease-free survival rate (31.3 mo) was 32% for control group as compared to 51.9% (28.3 mo) for chemotherapy group. There were more immediate adverse events in the chemotherapy arm than the radiotherapy arm.

Key words : *Cervical cancer, Radiotherapy, Chemotherapy.*

Reprint request : Lertsanguansinchai P, Department of Radiology , Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Received for publication. January 4, 1993.

* Department of Radiology, Faculty of Medicine, Chulalongkorn University.

ประเสริฐ เลิศสงวนสินชัย, สุรีย์ ฐิตะฐาน, ประยุทธ์ โรจน์พรประดิษฐ์, ประภัสสร รัชตะปิติ. การศึกษาเปรียบเทียบระหว่างการรักษามะเร็งปากมดลูกระยะที่ 2 บี, 3 บี โดยการใช้รังสีอย่างเดียวกับการใช้ ไมโตมัยซิน ซี และ 5-ฟลูออโรยูราซิล ร่วมกับรังสีรักษา. จุฬาลงกรณ์เวชสาร 2536 กรกฎาคม; 37(7) : 461-468

ตั้งแต่เดือนพฤศจิกายน 2531 ถึงเดือนกันยายน 2533 ผู้ป่วยมะเร็งปากมดลูก ที่ได้รับการวินิจฉัยว่าเป็นระยะที่ 2B และ 3B ที่หน่วยรังสีรักษา ภาควิชารังสีวิทยา โรงพยาบาลจุฬาลงกรณ์ จำนวน 52 ราย ถูกแบ่งการรักษาออกเป็น 2 กลุ่ม คือ ผู้ป่วยจำนวน 25 ราย ได้รับการรักษาด้วยรังสีอย่างเดียว และอีก 27 ราย ได้รับการรักษาด้วยรังสีร่วมกับการให้สารเคมีบำบัด Mitomycin C และ 5-FU. ผลการศึกษาพบว่า ไม่มีความแตกต่างในด้านการควบคุมโรคเฉพาะที่ แต่พบว่าอัตราการแพร่กระจายของโรคลดลงในกลุ่มที่ได้สารเคมีบำบัดร่วมด้วย อัตราเฉลี่ยการรอดชีวิต คิดเป็น 32% (31.3 เดือน) และ 51.9% (28.3 เดือน) ในกลุ่มที่ใช้รังสีอย่างเดียวและกลุ่มที่ให้สารเคมีบำบัดร่วมด้วย ตามลำดับ อย่างไรก็ตาม พบว่ามีผลข้างเคียงจากการรักษาในกลุ่มที่ให้สารเคมีบำบัดร่วมด้วยสูงกว่า กลุ่มที่ใช้รังสีอย่างเดียว

Carcinoma of the uterine cervix is the most common malignancy in Thailand.[1] It is also the leading cancer in females in Chulalongkorn Hospital.[2] The majority of cases present in the advanced stages IIB and IIIB.[3,4] By conventional radiotherapy alone, about 30-50% of cases failed in the pelvis and another 20-35% failed distantly.[3-4] Recently, systemic chemotherapy was used in these patients in order to improve the response rate and overall survival.[6-11] So, we conducted a clinical trial using concomittent chemoradiotherapy for patients with locally advanced stage IIB and IIIB cervical carcinoma. The aims of this study were to compare the response rate, the survival rate and adverse events between conventional radiotherapy and combination chemoradiotherapy groups.

Materials and methods

Between November 1988 and September 1990, 52 cases of FIGO stage IIB and IIIB uterine cervical cancer were simply randomized into 2 groups. There were 25 cases in the first group which were treated with conventional radiotherapy; and 27 cases in the second group treated with combination of conventional radiotherapy and mitomycin C plus oral 5-FU (Kyowa Hakko).

Criteria for patient eligibility

1. Histological proof of uterine cervical carcinoma
2. Previously untreated cases
3. Age $\leq$ 70 years
4. Hemoglobin > 10 gm%, white blood cell count >4,000/cumm platelet count > 100,000/cumm
5. Normal liver and renal functions
6. No evidence of cardiovascular and/or pulmonary diseases
7. No other malignancies
8. Karnofsky performance status $\geq$ 70%

Criteria for response and adverse events

CR (complete response) : the disappearance of all measurable or evaluable disease for at least 4 weeks

PR (partial response) : reduction of > 50% in sum of the products of two perpendicular diameters of all measurable lesions with no new lesions and persists for at least 4 weeks

Nc (No change) : a < 50% reduction and , 25% increase in the sum of the products of two perpendicular diameters of all measurable lesions with no new lesions.

PD (progressive disease) : a 25% or more increase in the products of two perpendicular diameters of any measured lesion or the appearance of new lesions.

During treatment tumour response was assessed by periodic pelvic and general physical examinations, routine laboratory tests, chest x-rays and CT scans as indicated, and biopsy in some cases. The response was determined immediately after completion of treatment and again two months later at a time of full radiation effects.

Adverse events criteria was graded accouding to ECOG adverse events criteria for acute and subacute adverse events, and kottmeier criteria for late gastrointestinal (GI) and genitourinary (GU) adverse events.

Definition of survival

Disease- Free Survival (DFS) was defined as the time from complete response to the first locoregional or distant recurrence.

Survival was calculated from the date of initiation of treatment until the date of death or last follow up.

Schedule of treatment

Conventional radiotherapy schedule consisted of whole pelvis irradiation, using Co-60 teletherapy or Linac 6-10 MV, midline tumour dose 3,000-5,000 cGy, with daily dose of 200 cGy, 5 fractions per week. After 10-14 days rest, the patients were treated with brachytherapy Ra-226 or Cs-137 remote after loading system (Selectron), one to two applications (two weeks apart) with a point A dose of 3,000-4,000 cGy.

For the combination group, mitomycin-C 10 mg/m 2 were administered intravenously on day 1 and day 29 and oral 5-FU (kyowa) 100 mg twice a day for 28 days simultaneously with the conventional radiotherapy schedule.

Results

The clinical characteristics of patients studied are showed in Table 1. The majority of the patients had squamous cell carcinoma and were in stage IIIB, The average TDF[12,13] at point A was 148 (range from 141 to 174) for the radiation alone group, and was 146 (range form 139 to 174) for the combination group.

Table 1. Clinical characteristics of patients.

	Radiation alone 25 cases	Combination group 27 cases
Mean age (range)	52 (36-69)	47.3 (30-62)
Mean Karnofsky performance stutus (range)	84% (70-90)	87.7% (70-90)
stage IIB	5	5
IIIB	20	22
Tumour size < 5 cm	13	15
> 5 cm	12	12
average (cm)	5.2 (3-8 cm)	4.4 (2-8 cm)
Type of lesion		
Exophytic	18	13
Ulcerative + infiltrative	7	14
Pathology		
large cell keratinizing squamous cell carcinoma	4	7
large cell non-keratinizing squamous cell carcinoma	12	9
small cell non-keratinizing squamous cell carcinoma	5	7
adenocarcinoma	4	4
TDF at point A	148(141-174)	146(139-174)
Median follow up in month (range)	31.3 (20-41)	28.3 (18-41)

The median follow-up time in the radiation alone group was 31.3 (range 20-41) months, and 28.3 (range 18-41) months in the combination group.

Response according to treatment modalities are showed in Table 2. There were two cases in the combination group excluded from the response evaluation due to early treatment related deaths. The response rate immediately after completion of treatment were 28% CR, 68% PR, 4% NC and 0% PD in radiation alone group as compared to 28% CR, 64% PR, 8% NC and 0% PD in combination group. While at two months follow-up the response rate were 64% CR, 16% PR, 0% NC and 20% PD in radiation alone group as compared to 84% CR, 4% PR, 0% NC and 12% PD in combination group.

Table 2. Response According to Treatment Modalities.

Response	Radiation alone		Combination group *	
	Immediate (a)	2 months (b)	Immediate (a)	2 months (b)
CR	7/25 (28%)	16/25 (64%)	7/25 (28%)	21/25 (84%)
PR	17/25 (68%)	4/25 (16%)	16/05 (64%)	1/25 (4%)
NC	1/25 (4%)	-	2/25 (8%)	-
PD	-	5/25 (20%)	-	3/25 (12%)

* Two cases in combination group were excluded due to early treatment related deaths.

a = immediately after completion of treatment

b = 2 months follow-up

The overall survival in radiation alone and combination groups were 40% and 59.3% respectively.

The disease-free survival in the radiation alone group was 32% in contrast to 51.9% in the combination group. Failure rate was more common in the radiation alone group, especially distant failure (Table 3.).

Table 3. Treatment results (18-41 month of follow up).

	Radiation alone (N = 25) Cases (%)	Combination group (N = 27) Cases (%)
Overall survival	10 (40%)	16 (59.3%)
Disease-free survival	8 (32%)	14 (51.9%)
Loss to follow up	3 (12%)	3 (11%)
Locoregional failure alone	5 (20%)	5 (18.5%)
Locoregional with distant failure	2 (8%)	-
Distant failure alone	7 (28%)	1 (3.7%)

Table 4 shows the results of acute and subacute adverse event, according to ECOG toxicity criteria. The majority of acute hematotoxicity and acute non-hematotoxicity were in grade I-II and were more common in the combination group. There were also two early treatment related deaaths (septic shock) in the combination group.

Table 4. Acute and subacute adverse events (ECOG criteria).

	Radiation alone (25 cases) cases (%)	Combination groups (27 cases) cases (%)
Acute Hematotoxicity		
Anemia grade I-II	10/25 (40%)	17/27 (63%)
grade III	-	-
grade IV	-	-
Neutropenia grade I-II	5/25 (20%)	17/27 (63%)
grade III	-	-
grade IV	-	2/27 (7.4%)
Thrombocytopenia grade I-II	-	2/27 (7.4%)
grade III	-	-
grade IV	-	-
Acute non-hematotoxicity		
Nausea/vomiting grade I-II	6/25 (24%)	12/27 (44.4%)
grade III	-	-
grade IV	-	-
Diarrhea grade I-II	9/25 (36%)	17/27 (63%)
grade III	-	-
grade IV	-	-
Hematuria grade I-II	1/25 (4%)	-
grade III	-	-
grade IV	-	-

Table 5. showed the results of late adverse events, according to the Kottmeier criteria.[14] The majority of late complications were grades I-II proctitis and/or cystitis which were equal in both groups. There was one severe late complication (rectovagina fistula which required a colostomy) in the combination group.

Table 5. Late adverse events (kottmeier criteria).

Late toxicity	Radiation alone Cases (%)	Combination group Cases (%)
Proctitis grade I	5/25 (20%)	6/27 (22.2%)
grade II	2/25 (8%)	1/27 (37%)
grade III	-	1/27 (3.7%)
Cystitis grade I	4/25 (10%)	5/27 (18.5%)
grade II	-	-
grade III	-	-

Discussion

There were many reports about the use of chemotherapeutic agents in patients with carcinoma of the cervix.[6-11] Some reports showed improvement in the survival rate.[6,10,15] In our study we used mitomycin C and 5-FU concurrently with conventional radiotherapy in locally advanced cervical carcinoma. For the treatment results, the combination group showed better disease-free survival as compared to the radiation alone group (51.9% VS 32%). This may be due to the decrease in locoregional recurrence (18.5% VS 28%) and especially distant metastases (3.7% VS 36%). However, this study showed more frequent and severe immediate bone marrow suppression in the combination group. There were also 2 early treatment related deaths from acute septic shock during the third and fourth week of treatment in the combination group. The majority of late gastro-intestinal and genitourinary tract systems adverse events were tolerable (Grade I-II). Only one patient in the combination group developed rectovaginal fistula which required a colostomy. The authours found that the use of mitomycin-C intravenously and oral 5-FU tablets given concurrently with conventional irradiation improved the disease-free survival. Nevertheless, there were more acute and late adverse events in the combination group. Currently, we are developing appropriate doses and schedules of chemotherapy in order to improve the treatment outcome and minimize acute and late adverse events in treating patients with locally advanced carcinoma of the uterine cervix.

Summary

Mitomycin C and 5-FU in combination with radiotherapy showed advantages in locally advanced stage IIB and IIIB cancer of the uterine cervix. The disease free survival in the combination group was 51.9% as compared to 32% in the radiation alone group. There were more frequent acute hematotoxicity and slightly more late gastrointestinal and genitourinary tract adverse events in the chemotherapy arm.

References

1. National Cancer Institute, Department of Medical service, Ministry of Public Health, Cancer statistic 1976-1984
2. Chulalongkorn University Hospital, Faculty of Medicine, Tumor registry statistical report. 1983-1989
3. Lertsanguansinchai P, Kamphu Na Ayudhya P, Thitathan S, Rajatapiti P, Rojpornpradit P. Treatment of carcinoma of the cervix with Co-60 and Cs-137. Chula Med J 1989 Mar; 33(3) : 195-205
4. Lertsanguansinchai P, Rojpornpradit P, Thitathan S, Rajatasiti P, Kambhu Na Ayudlya P. Analysis of 515 cases of cervical carcinoma treated with radiotherapy at Chulalongkorn hospital. Chula Med J 1990 Jan; 34(1) : 31-40
5. Brady LW, Markoc AM, De EULis T, Lewis GC Jr. Treatment of advanced and recurrent gynecologic cancer. Cancer 1987 Oct; 60(8) : 2081-93
6. Mathew CP. Single Massive Dose Mitomycin C in Advanced Malignancy. Mitomycin in Clinical Oncology, Kyo : Hakko Kogyo, 1981. 83-94
7. John M, Cooke JK, Flam M, Cadmanabhan A, Mowry PA. Preliminary results of concomitant radiotherapy in advanced cervical carcinoma. Gynecol Oncol 1987 Sep; 28(1) : 101-10
8. Thomas G, Dembo A, Beale F, Beam H, Bush R, Herman J. Concurrent radiation, mitomycin-C and 5-Fluorouracil in poor prognosis carcinoma of the cervix : Preliminary results of a phase I-II study. Int J Radiat Oncol Biol Phys 1984 Sep; 10(9) : 1785-90
9. Lorvidhaya V, Charoeniam V, Tonusin A, Plogleumsang D, Issariyodom P. Induction chemotherapy and irradiation in advanced cervical carcinoma. Thai J Radiol 1986 Apr; 23(2) : 97-101
10. Saipin T. Comparison of conventional irradiation and irradiation Mitomycin C combination in stage II uterine cervical cancer. Thai J Radiol 1992 Apr; 29(1) : 11-6
11. Rosenthal CJ, Khulpateca A, Boyce J, Mehrotra S, Tamarin S. Effective chemotherapy for advanced carcinoma of cervix with Bleomycin, Cisplatin and Methotrexate. Cancer 1983 Nov; 52(11) : 2025-30
12. Orton CG, Ellis F. Time-dose (Factors 75-80 (TDFS) in brachytherapy. Br J Radiol 1947 Sep; 47(561) : 603-7
13. Orton CG, Ellis F. A simplification in the use of the NSD concept in practical radiotherapy. Br J Radiol 1973 Jul; 46(547) : 529-37
14. Kottmeier HL. Complication following radiation therapy in carcinoma of the cervix and their treatment. Am J Obstet Gynecol 1964; 848-54
15. Roch-Berry CSB. Vincristine, Bleomycin and Mitomycin-C for the treatment of cervical carcinoma. Mitomycinû85 clinic- Pharmacology Perspective Symposium in Frankfurt, November 1985.