# Comparative Study of Bulky Stage IB and IIA Cervical Cancer Patients Treated by Radical Hysterectomy with and without Neoadjuvant Chemotherapy : Long-Term Follow-up

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**Abstract**

One hundred and ninety patients with bulky (> 3 cm) stage IB and IIA cervical cancer who underwent radical hysterectomy between 1991 and 1994 at Maharaj Nakorn Chiang Mai Hospital were reviewed to determine whether neoadjuvant chemotherapy (NAC) with MVAC (Methotrexate, Vinblastine, Adriamycin, Cisplatin) improved survival. There were 42 patients treated with pre-operataive NAC (MVAC 1-3 courses) and 148 patients treated by primary surgery (PS). In the NAC group, the overall response rate from MVAC was 88.1 per cent with 31.0 per cent having complete clinical response and 7.1 per cent with complete pathological response. Pelvic lymph node metastasis was not significantly different between the NAC group (16.7%) and the PS group (18.2%). At a median follow-up of 64.5 months, 19.0 per cent in the NAC group and 18.2 per cent in the PS group had tumor recurrence. The 5-year progression free and overall survival was 80.8 per cent and 92.0 per cent respectively for the NAC group which was not significantly different from 80.2 per cent and 92.9 per cent respectively in the PS group. In conclusion, although NAC can decrease the tumor size and produce a high response rate, it does not improve survival in bulky stage IB and IIA cervical cancer patients.

**Key word** : Chemotherapy, Cervical Cancer, Survival

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Cervical cancer is the most common gynecologic malignancy in developing countries. Despite remarkable improvement in the clinical management, the survival rate for the distinct stage has not improved[1,2]. In non bulky stage IB or IIA cervical cancer, treatment with either radical surgery or radiation produces a high curative rate[3-6] with 5-year survival of 80-90 per cent[7,8]. However; in bulky tumor, the 5-year survival rate is only 50-70 per cent[7,8].

Over the past 15 years, there has been much interest in neoadjuvant chemotherapy for cervical cancer. Several authors have reported excellent response rates, improved operability and decreased pelvic node metastasis[9-13]. However, long-term follow-up was limited and the overall impact on recurrence and survival remains unclear.

The authors report the long-term follow-up of bulky stage IB and IIA cervical cancer patients treated with pre-operative neoadjuvant chemotherapy using MVAC (Methotrexate, Vinblastine, Adraimycin and Cisplatin) in comparison to those who underwent radical surgery without neoadjuvant chemotherapy.

## MATERIAL AND METHOD

The authors retrospectively evaluated all patients with bulky (> 3 cm) stage IB and IIA cervical cancer who underwent radical hysterectomy with pelvic and paraaortic lymphadenectomy at Maharaj Nakorn Chiang Mai Hospital between Januray 1991 and December 1994. There were altogether 190 patients who fitted the criteria. Of these patients, 42 were treated with neoadjuvant chemotherapy followed by radical surgery (NAC group) and 148 underwent radical surgery without any previous treatment. (primary surgery : PS group).

In the NAC group, patients received 1-3 courses of MVAC chemotherapy before surgery. Each cycle of chemotherapy was administered every 4 weeks. The dose and schedule of chemotherapy are shown in Table 1.

**Table 1. Dose-schedule of MVAC chemotherapy.**

| | | |
|---|---|---|
| Methotrexate | 30 mg/m$^2$ IV | Day 1, 15, 22 |
| Vinblastine | 2 mg/m$^2$ IV | Day 2, 15, 22 |
| Adriamycin | 30 mg/m$^2$ IV | Day 2 |
| Cisplatin | 70 mg/m$^2$ IV | Day 2 |

Clinical response to chemotherapy was evaluated before each cycle and before surgery. Response was considered "complete" if no clinical evidence of tumor was noted, and "partial" if the tumor size was reduced to more than 50 per cent. "Stable disease" was defined as less than 50 per cent reduction in the tumor size. Complete pathological response was defined as no residual tumor on any surgical specimen of a patient with complete clinical response. The time interval from the last day of chemotherapy to the day of surgery ranged from 14 - 50 days with the median of 29 days.

All patients underwent the same operative procedure (class III radical hysterectomy with pelvic and paraaortic node dissection) by gynecologic oncologists. Those who had pelvic node metastasis or parametrial involvement received post-operative adjuvant pelvic radiotherapy. In general, the dose of post-operative adjuvant radiotherpy was 5000 cGy.

After completion of treatment, patients were examined every 3-4 months for the first 2 years and every 6 months for another 3 years. After 5 years of uncomplicated follow-up, the patients were examined once a year. Physical and pelvic examination were performed at every visit. Evidence of recurrence was confirmed by cytologic or histologic examination if possible. Chest X-ray and CT scan were done when appropriate. Patients were followed until death or last follow-up. Overall survival was calculated from the first day of treatment to the time of death. Progression free survival was calculated from the first day of treatment to the time of tumor progression or recurrence.

For the statistical analysis, Chi squares or Fisher's exact test were used for categorial variables. Wilcoxan rank sum test was used for continuous variables. Survival analysis was evaluated by Kaplan-Meier product limit method and the difference of survival curves was compared by the log-rank test. A two-tailed p value of less than 0.05 was considered significant.

## RESULTS

Analyses were based on 190 patients ; 42 in the NAC group and 148 in the PS group. The pre-treatment characteristics are listed in Table 2. Patients' age, tumor stage and histology were not significantly different between the two groups. Tumor size in the NAC group was significantly larger and the gross appearance of the lesion in

**Table 2. Patients' basic characteristics.**

| | PS (n=148) | % | NAC (n=42) | % | p |
|---|---|---|---|---|---|
| Age (year) mean ± SD | 40.3 ± 7.2 | | 38.6 ± 8.0 | | 0.190 |
| Tumor size (cm) mean ± SD | 4.3 ± 0.9 | | 4.8 ± 1.6 | | 0.012 |
| FIGO stage | | | | | 0.169 |
| IB | 128 | 86.5 | 32 | 76.2 | |
| IIA | 20 | 13.5 | 10 | 23.8 | |
| Histology | | | | | 0.096 |
| Squamous cell carcinoma | 116 | 78.4 | 27 | 64.3 | |
| Non squamous cell carcinoma | 32 | 21.6 | 15 | 35.7 | |
| Adenocarcinoma | 19 | 12.8 | 11 | 26.2 | |
| Adenosquamous | 6 | 4.1 | 4 | 9.5 | |
| Anaplastic - neuroendocrine | 7 | 4.8 | 0 | 0 | |
| Tumor characteristics | | | | | 0.049 |
| Exophytic | 71 | 48.0 | 28 | 66.7 | |
| Ulceroinfiltrative | 77 | 52.0 | 14 | 33.3 | |

**Table 3. Tumor response to chemotherapy according to various factors.**

| Characteristics | Number of patients | Response | % | p |
|---|---|---|---|---|
| Age | | | | 0.639 |
| ≤ 40 years | 27 | 23 | 85.2 | |
| > 40 years | 15 | 14 | 93.3 | |
| Stage | | | | 1.000 |
| IB | 32 | 28 | 87.5 | |
| IIA | 10 | 9 | 90.0 | |
| Gross appearance | | | | 0.650 |
| Exophytic | 28 | 24 | 87.5 | |
| Ulceroinfiltrative | 14 | 13 | 92.9 | |
| Histology | | | | 0.047 |
| Squamous | 27 | 26 | 96.3 | |
| Non squamous | 15 | 11 | 73.3 | |
| Tumor differentiation | | | | 0.015 |
| Grade I | 6 | 3 | 50.0 | |
| Grade II-III | 36 | 34 | 94.4 | |
| Tumor size | | | | 0.656 |
| ≤ 5 cm | 22 | 20 | 90.9 | |
| > 5 cm | 20 | 17 | 85.0 | |
| Total | 42 | 37 | 88.1 | |

the NAC group was mainly exophytic lesion while ulceroinfiltrative lesions were more common in the PS group.

After treatment with MVAC for 1-3 courses (33 received only 1 course, while 5 and 4 patients received 2 and 3 courses respectively), complete clinical response was observed in 13 patients (31.0%) in which 3 (7.1%) had complete pathological response. Partial response was seen in 24 patients (57.1%) while 5 (11.9%) had stable disease. MVAC chemotherapy reduced the mean tumor size from 4.8 ± 1.6 cm to 1.6 ± 1.6 cm. Table 3 demonstrates the correlation between various factors and tumor response to chemotherapy. Only tumor histology and tumor differentiation influenced the effectiveness of chemotherapy. Squamous cell carcinoma and tumors with moderate or poor differentiation had a significantly higher response rate compared to non-squmous cell carcinoma and well differentiated tumors.

**Table 4. Comparison of nodal metastasis, parametrial involvement and tumor recurrence between patients in the NAC and PS group.**

| | PS (n=148) | % | NAC (n=42) | % | P value |
|---|---|---|---|---|---|
| Lymph node metastasis | 27 | 18.2 | 7 | 16.7 | 0.994 |
| Parametrial involvement | 5 | 3.3 | 0 | 0 | 0.588 |
| Tumor recurrence | 27 | 18.2 | 8 | 19.0 | 1.000 |
| Distant recurrence | 8 | 29.6 | 2 | 25.0 | 1.000 |

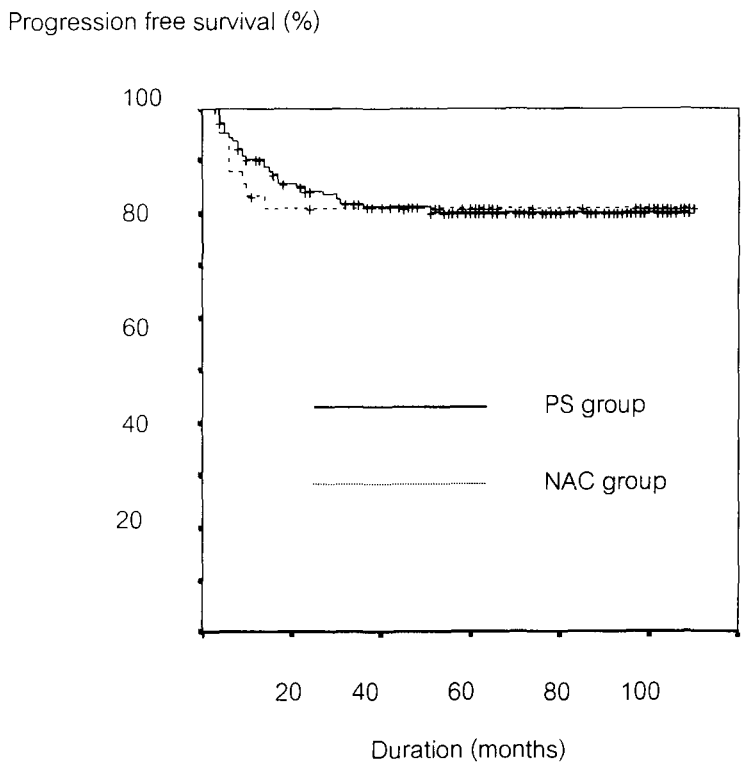


**Fig. 1. Progression free survival between the NAC and the PS groups.**

Considering the adverse effect of chemotherapy; from 55 courses of MVAC, there were no grade 3-4 leukopenia or thrombocytopenia, only 1 patient had grade 3 anemia. However, all patients had grade 3 or 4 alopecia.

Although patients who received neoadjuvant chemotherapy had larger tumors than those who did not receive neoadjuvant treatment, the incidence of pelvic node metastasis (16.7% *vs* 18.2%) and parametrial involvement (0% *vs* 3.3%) were not significanly different between the two groups. (Table 4)

With the median follow-up of 64.5 months, tumor recurrence occurred in 8 patients (19.0%) in the NAC group and 27 (18.2%) in the PS group. The incidence of distant recurrence was not significantly different between the two groups. (Table 4) Fourteen patients died during the follow-up period, 12 of which were from cervical cancer. Comparison of progression free survival and overall survival of

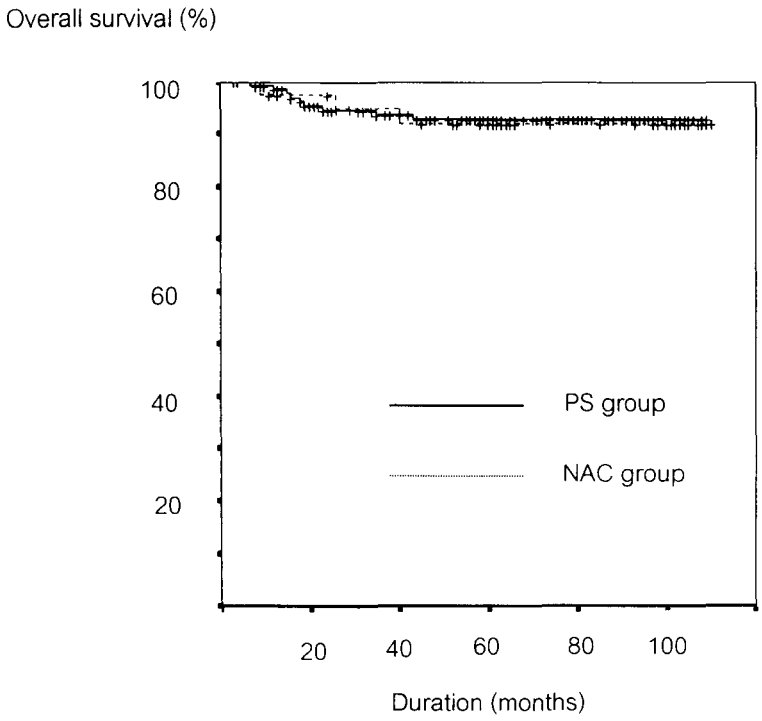


**Fig. 2. Overall survival between the NAC and the PS groups.**

patients who received and did not receive chemotherapy is shown in Fig. 1 and 2. Five-year progression free survival and overall survival were 80.9 per cent and 92.0 per cent respectively in the NAC group which was not significantly different from 80.2 per cent and 90.9 per cent respectively in the PS group.

It seems that chemotherapy, though having an impressive response in decreasing tumor size, can neither decrease the rate of nodal metastases nor increase the survival.

## DISCUSSION

Bulky early stage cervical cancer is still a treatment problem because standard treatment of either radiotherapy or radical surgery offers a rather low survival rate of 50-70 per cent[7-8]. This result has led to other treatment modalities to increase survival. One of the interesting modalities in the treatment of bulky early-stage cervical cancer is neoadjuvant chemotherapy followed by radical surgery. Many authors reported that this modality yielded a very high response rate[9-13]. However, the issue of whether it can improve treatement outcome is still inconclusive since most studies had a small number of patients, short follow-up period and no group for comparison. To our knowledge, so far only 3 studies (1 randomized[14] and 2 nonrandomized studies[15,16]) have evaluated the benefit of neoadjuvant chemotherapy before radical surgery in bulky early stage cervical cancer compared to the control group who underwent radical surgery.

The randomized trial of Sardi et al studied cervical cancer patients who had squamous cell carcinoma in stage IB with a tumor size larger than 2 cm only. All patients in this study received postoperative adjuvant radiotherapy and the result demonstrated that patients who benefited from neoadjuvant chemotherapy were the subgroup with a tumor size of more than 4 cm but not the subgroup with a tumor size between 2-4 cm. The 5 year survival rate in the neoadjuvant chemotherapy group

who had a tumor size larger than 4 cm (61 patients) was 80 per cent compared to 61 per cent in the control group (56 patients)[14].

The nonrandomized studies of Namkoong et al[15] and Serur et al[16] showed that bulky cervical cancer stage IB tended to benefit from neoadjuvant chemotherapy because the pateints who received chemotherapy had a higher, though not significant, survival rate.

The present study, unlike the 3 previous studies, could not demonstrate that neoadjuvant chemotherapy had significant benefit in bulky early stage cervical cancer. The five-year progression free survival in the neoadjuvant chemotherapy group was 80.9 per cent, compared to 80.2 per cent in the control group. (Fig. 1)

The explanation of no survival benefit of the neoadjuvant chemotherpy in the present study may be from the bias in selecting patients in this group as it was not a randomized study. Patients in the neoadjuvant chemotherapy group had a significantly larger tumor size which tended to have worse prognosis. It is known that patients with stage IIA have a worse prognosis than those with stage IB[17] and nonsquamous cell carcinoma has a worse prognosis than squamous cell carcinoma[18-20]. In the present study, there were more, though not significant, patients with stage IIA and nonsquamous cell carcinoma in the neoadjuvant chemotherapy group (Table 2) Moreover, nonsquamous cell carcinoma has a lower response rate to chemotherapy as confirmed by the present study (Table 3) and the study of Namkoong et al[15].

Another reason may be from the dose-schedule of the chemotherapy. In the present study most patients received MVAC chemotherapy for only 1 course while in the previous 3 studies[14-16] most of the patients received PVB (Cisplatin - Vinblastine - Bleomycin) for 3 courses. However, regarding the response rate, our chemotherapy regimen yielded a high response rate of 88.1 per cent which is comparable to 83 per cent - 90 per cent in other studies[14-16]. The complete clinical response and complete pathological response rate were 31.0 per cent and 7.1 per cent respectively, which is also comparable to 10-28 per cent and 4.6-6 per cent in other studies[10,15,16,21].

Pelvic node involvement, which is known to be the most significant prognostic factor for survival[22-24] was also claimed to decrease in patients who received neoadjuvant chemothrapy[14-16]. In the present study, the incidence of pelvic node metastasis was not significantly different between the NAC and PS groups (16.7% *vs* 18.2%).

Although most studies seem to promote the benefit of neoadjuvant chemotherapy before radical surgery in bulky early stage cervical cancer, the recent randomized study of Chang[21] could not demonstrate difference in the 5 year survival in bulky stage IB/IIA cervical cancer patients (including squamous, adenocarcinoma and adenosquamous cell carcinoma) between those receiving neoadjuvant chemotherapy followed by radical surgery (70%) and those receiving standard treatment with radiotherapy (61%). Patients in the NAC group in the present study had a comparable pelvic node metastasis rate and survival rate to the PS group. Chemotherapy may have some benefit, since patients in the NAC group had a larger tumor size and more poor prognostic factors which, in general, should have a higher pelvic node metastasis rate and lower survival rate than the PS group.

In conclusion, neoadjuvant chemotherapy may benefit selected groups of patients with bulky squamous cell carcinoma of the cervix. A prospective randomized trial is required to confirm the benefit of neoadjuvant chemotherapy before radical surgery in patients with early-stage cervical cancer especially the squamous cell type and a tumor size larger than 4 cm.

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## REFERENCES


1. Petterson F ed. Annual report on the results of 'reatment in gynecological cancer. Stockholm, 1991; 20: 1-8.
2. Petterson F ed. 22nd annual report on the results of treatment in gynecological cancer. Stockholm, FIGO, 1994; 22: 1-10.
3. Landoni F, Maneo A, Colombo A, et al. Randomised study of radical surgery *versus* radiotherapy for stage IB-IIA cervical cancer. Lancet 1997; 350: 535-40.
4. Roddick JR Jr, Greenlaw RH. Treatment of cervical cancer : A randomized study of operation and radiation. Am J Obstet Gynecol 1971; 109: 754-64.
5. Newton M. Radical hysterectomy or radiotherapy for stage I cervical cancer. A prospective comparison with five and ten year follow-up. Am J Obstet Gynecol 1975; 123: 535-43.
6. Morley GW, Seski JC. Radical pelvic surgery *versus* radiation therapy for stage I carcinoma of the cervix (exclusive of microinvasive). Am J Obstet Gynecol 1976; 126: 785-98.
7. Piver M, Chung W. Prognostic significance of cervical lesion size and pelvic node metastasis in cervical carcinoma. Obstet Gynecol 1975; 46: 507-10.
8. Delgado G, Bundy B, Zaino R, Sevin BU, Creasman WT, Major F. Prospective surgical pathologic study of the disease free interval in patients with stage IB squamous cell cancer of the cervix. Gynecol Oncol 1990; 38: 352-7.
9. Benedetii-Panici P, Greggi S, Scambia G, et al. High-dose cisplatin and bleomycin neoadjuvant chemotherapy plus radical surgery in locally advanced cervicaal carcinoma. A preliminary report. Gynecol Oncol 1991; 41: 212-6.
10. Chang HC, Lai CH, Chou PC, et al. Neoadjuvant chemotherapy with cisplatin, vincristine and bleomycin and radical surgery in early staage bulky cervical carcinoma. Cancer Chemother Pharmacol 1992; 30: 281-5.
11. Dottino PR, Plaxe SC, Beddoe AM, et al. Induction chemotherapy followed by radical surgery in cervical cancer. Gynecol Oncol 1991; 40: 7-11.
12. Eddy GL, Manetta A, Alvarez RD, et al. Neoadjuvant chemotherapy with vincristine and cisplatin followed by radical hysterectomy and pelvic lymphadenectomy for FIGO stage Ib bulky cervical cancer: A Gynecologic Oncology Group pilot study. Gynecol Oncol 1995; 57: 412-6.
13. Fontanelli R, Spatti G, Raspagliesi F, et al. A prospective single course of high dose cisplatin and bleomycin with gluththion in bulky stage Ib/II carcinoma of the cervix. Ann Oncol 1992; 3: 117-21.
14. Sardi JE, Giaroli A, Sananes C, et al. Long-term follow-up of the first randomized trial using neoadjuvant chemotherapy in stage Ib squamous cell carcinoma of the cervix. Gynecol Oncol 1997; 67: 61-9.
15. Namkoong SE, Park JS, Kim JW, et al. Comparative study of the patients with locally advanced stage I and II cervical cancer treated by radical surgery with and without pre-operative adjuvant chemotherapy. Gynecol Oncol 1995; 59: 136-42.
16. Serur E, Mathews RP, Gates J, et al. Neoadjuvant chemotherapy in stage IB2 squamous cell carcinoma of the cervix. Gynecol Oncol 1997; 65: 348-56.
17. Fuller AF Jr, Elliott N, Kosloff C, Hoskins WJ, Lewis JL Jr. Determinants of increased risk for recurrence in patients undergoing radical hysterectomy for stage IB and IIA carcinoma of the cervix. Gynecol Oncol 1989; 33: 34-9.
18. Hopkins MP, Morley GW. A comparison of adenocarcinoma and squamous cell carcinoma of the cervix. Obstet Gynecol 1991; 77: 912-7.
19. Burke TW, Hoskins WJ, Heller PB, Bibro MC, Weiser EB, Park PC. Prognostic factors associated with radical hysterectomy failure. Gynecol Oncol 1987; 26: 153-9.
20. Larson DM, Copeland LJ, Stringer CA, Gershenson DM, Malone JM Jr, Edwards CL. Recurrent cervical carcinoma after radical hysterectomy. Gynecol Oncol 1988; 30: 381-7.
21. Chang T, Laai C, Hong J, et al. Randomized trial of neoadjuvant cisplatin, vincristine, bleomycin, and radical hysterectomy *versus* radiation therapy for bulky stage IB and IIA cervical cancer. J Clin Oncol 2000; 18: 1740-7.
22. Zaino RJ, Ward S, Delgado G, et al. Histopathologic predictors of the behavior of surgically treated stage IB squamous cell carcinoma of the cervix. A Gynecologic Oncology Group Study. Cancer 1992; 69: 1750-8.
23. Lai CH, Chang HC, Chang TC. Prognostic factors and impacts of adjuvant therapy in early stage cervical carcinoma with pelvic node metastases. Gynecol Oncol 1993; 51: 390-6.
24. Sevin BU, Nadji M, Lampe B, Lu Y. Prognostic factors of early stage cervical cancer treated by radical hysterectomy. Cancer 1995; 76 (Suppl): 1978-86.

# ผลการรักษาระยะยาวของผู้ป่วยมะเร็งปากมดลูกระยะ IB และ IIA เปรียบเทียบระหว่างกลุ่มที่ได้รับเคมีบำบัดและไม่ได้รับเคมีบำบัดก่อนการผ่าตัด radical hysterectomy

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รายงานนี้เป็นการศึกษาถึงประโยชน์ของเคมีบำบัดว่าจะสามารถเพิ่มอัตราการอยู่รอดในผู้ป่วยมะเร็งปากมดลูกระยะ IB และ IIA ที่มีก้อนมะเร็งขนาดใหญ่ได้หรือไม่ โดยทำการศึกษาย้อนหลังผู้ป่วยมะเร็งปากมดลูกระยะ IB และ IIA ที่มีก้อนมะเร็งขนาดใหญ่กว่า 3 ซม. จำนวน 190 ราย ที่ได้รับการผ่าตัด radical hysterectomy ระหว่างปี 2534–2537 ที่โรงพยาบาลมหาราชนครเชียงใหม่ โดยที่ผู้ป่วย 148 รายไม่เคยได้รับการรักษาใดก่อนการผ่าตัด ส่วนผู้ป่วย 42 รายได้รับเคมีบำบัดก่อนการผ่าตัด 1–3 ครั้ง เคมีบำบัดที่ให้คือ MVAC regimen ซึ่งประกอบด้วย Methotrexate, Vinblastine, Adriamycin และ Cisplatin ผู้ป่วยที่ได้รับเคมีบำบัด 88.1% มีการตอบสนองต่อเคมีบำบัด โดย 31.0% ก้อนมะเร็งยุบไปหมดจนไม่สามารถตรวจพบด้วยตาเปล่า และ 7.1% การตรวจทางพยาธิวิทยาไม่พบมะเร็ง จากการเปรียบเทียบระหว่างกลุ่มที่ได้รับและไม่ได้รับเคมีบำบัด พบว่าอัตราการกระจายไปต่อมน้ำเหลืองไม่แตกต่างกันคือ 16.7% และ 18.2% ตามลำดับ หลังจากติดตามผู้ป่วยเป็นเวลาเฉลี่ย 64.5 เดือน พบว่าอัตราการกลับเป็นซ้ำ (19% และ 18.2%) และอัตราการอยู่รอด 5 ปี (92.0% และ 92.9%) ไม่แตกต่างกัน โดยสรุป เคมีบำบัดสามารถลดขนาดของก้อนมะเร็งปากมดลูกได้อย่างมีนัยสำคัญทางสถิติ แต่ไม่ช่วยให้อัตราการอยู่รอดของผู้ป่วยมะเร็งปากมดลูกสูงขึ้น

**คำสำคัญ** : เคมีบำบัด, มะเร็งปากมดลูก, อัตราการอยู่รอด

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