Journal of Cancer Therapy, 2015, 6, 1075-1082
Published Online November 2015 in SciRes. http://www.scirp.org/journal/jct
http://dx.doi.org/10.4236/jct.2015.612117

Treatment Results of Adjuvant Chemotherapy after Radical Hysterectomy for Intermediate-Risk Stage IB-IIB Cervical Cancer

Hongwu Wen[1*], Tongyu Liu[2], Zhaoyi Feng[1], Weiping Huang[3], Ke Ma[4], Xia Tao[1]

[1]Department of Obstetrics and Gynecology, Peking University First Hospital, Beijing, China
[2]Department of Gynecology, Fujian Provincial Tumor Hospital, Fuzhou, China
[3]Department of Obstetrics and Gynecology, The Fifth Hospital of Shijiazhuang, Shijiazhuang, China
[4]Department of Obstetrics & Gynecology, Beijing Tsinghua Changgung Hospital Medical Center, Tsinghua University, Beijing, China
Email: *wenhongwu3184@sohu.com

Received 24 October 2015; accepted 23 November 2015; published 26 November 2015

Abstract

Objective: The objective is to evaluate the effectiveness of chemotherapy as postoperative adjuvant therapy for stage IB-IIB cervical cancer with intermediate-risk factors. Methods: We retrospectively reviewed the medical records of 119 cervical cancer patients with intermediate-risk factors treated with radical hysterectomy and pelvic lymphadenectomy from December 1997 to September 2010. The intermediate-risk factors included bulky tumor (≥4 cm), lymphovascular space invasion, and deep stromal invasion. Sixteen patients did not receive adjuvant therapy (observation group); 73 were treated with chemotherapy (CT group); 30 were treated with adjuvant radiation therapy (RT group). The significance of the clinical parameters, 3- and 5-year overall survival (OS) rates of each group, was analyzed. Results: The 3- and 5-year OS rates between the observation group and adjuvant therapy group (CT plus RT groups) were not statistically different (3-year OS: 100% and 94.4%, respectively; 5-year OS: 100% and 92.3%, respectively; $p > 0.05$). The 3- and 5-year OS rates between the CT group and RT group were also not statistically different (3-year OS: 93.6% and 96.4%, respectively; 5-year OS: 80.7% and 96.4%, respectively; $p < 0.05$). Univariate and multivariate analysis of survival indicated that different adjuvant therapies were not independent prognostic indicators for IB-IIB cervical cancer patients with intermediate-risk factors. Conclusions: CT may have equivalent therapeutic effect as RT for stage IB-IIB cervical cancer patients with intermediate-risk factors after radical surgery, and prospective randomized

*Corresponding author.

How to cite this paper: Wen, H.W., Liu, T.Y., Feng, Z.Y., Huang, W.P., Ma, K. and Tao, X. (2015) Treatment Results of Adjuvant Chemotherapy after Radical Hysterectomy for Intermediate-Risk Stage IB-IIB Cervical Cancer. *Journal of Cancer Therapy*, **6**, 1075-1082. http://dx.doi.org/10.4236/jct.2015.612117

trial is needed to study the effect of CT in these patients.

Keywords

Cervical Cancer, Chemotherapy, Radiotherapy, Prognosis

1. Introduction

Radiotherapy (RT) is widely accepted as postoperative adjuvant therapy for reducing recurrence in patients with cervical cancer. Intermediate-risk factors for recurrence after radical hysterectomy include lymphovascular space invasion (LVSI), tumor size ≥ 4 cm, and deep stromal invasion (DSI) [1]. According to the International Federation of Gynecology and Obstetrics (FIGO) clinical practice guidelines for gynecological cancers (2010) and National Comprehensive Cancer Network (NCCN) cervical cancer guidelines (2013), adjuvant treatment for patients with these intermediate-risk factors includes observation and RT with or without cisplatin-based chemotherapy (CT). However, premature ovarian failure is an important and common long-term side effect after curative RT, especially in young patients. Neoadjuvant CT is effective for treating cervical cancer. Therefore, chemotherapy is expected to play therapeutical effect and may be recommended for patients with intermediate-risk factors, especially young patients. However, there are only a few reports on the effectiveness of adjuvant CT in patients with intermediate-risk factors after radical surgery. The aim of this study was to compare the outcome of CT and radiation as adjuvant therapy for patients with FIGO stage IB-IIB cervical cancer and surgically confirmed intermediate-risk factors.

2. Materials and Methods

2.1. Subjects

This retrospective study was performed at the Department of Obstetrics and Gynecology of Peking University First Hospital (Beijing, China). One hundred and nineteen patients diagnosed with stage IB-IIB cervical cancer from December 1997 to September 2010 were reviewed retrospectively. All patients underwent radical hysterectomy with removal of a vaginal cuff of at least 3 cm, total resection of parametrial tissue, and systematic pelvic lymphadenectomy. Whether bilateral adnexectomy was performed depended on the age and wishes of the patient. Neoadjuvant interventional CT was administered to 50 patients of squamous cell carcinoma (SCC) with tumors > 4 cm. The BIP regimens consisted of bleomycin (20 mg/m^2) and cisplatin (70 mg/m^2), followed by five consecutive daily infusions of ifosfamide (2 g/day). Of the 119 patients, 16 did not receive any adjuvant therapy (observation group); 73 were treated with CT (CT group); and 30 were treated with RT (RT group).

2.2. Assessment of Intermediate-Risk Factors

All patients had at least one intermediate-risk factor for recurrence, including LVSI, tumor size ≥ 4 cm, and DSI (>1/2 cervical invasion). These patients were examined preoperatively and staged according to FIGO standard. Tumor diameter was assessed by inspection and palpation. Three pathologists determined and reviewed the pathological criteria with agreement based on the opinion of two or more pathologists. Stromal invasion depth was measured by the halved fractional thickness of the cervical wall. Lymphovascular involvement was determined by the presence or absence of tumor cells in the lymphovascular space on the surgical specimen.

2.3. Adjuvant Therapy

As postoperative adjuvant therapy, CT and RT were introduced sufficiently to patients with intermediate-risk factors. Therapeutic choice was made by the patients. Sixteen patients chose observation for reasons such as economic problems and fear of CT or RT. Seventy-three patients accepted postoperative CT which was administered every three weeks. CT regimen was the same as neoadjuvant CT for SCC, otherwise, for adenocarcinomas, taxol 135 mg/m^2 and carboplatin AUC5 were administered as postoperative CT regimen. Thirty patients accepted postoperative RT which was administered by the Department of Radiotherapy of Peking University

First Hospital. The total dose for the whole pelvis was 50 Gy with opposing anterior and posterior fields, or a 4-field anterior-posterior and lateral technique.

2.4. Follow-Up and Statistical Analysis

All patients were followed up for a median 43 months (range: 20 - 182 months). The Statistical Package for Social Sciences (SPSS, Chicago, IL) was used for analysis; statistical significance was defined as $p < 0.05$. The chi-square test, Student *t*-test, and Fisher exact test were used for statistical analysis of the patient characteristics. The Kaplan-Meier method and log-rank test were used for determining the survival distribution and differences in each group. The Cox regression model was used for multivariate analyses of prognostic factors.

3. Results

3.1. Patient Characteristics

Comparison of the observation group with the adjuvant therapy group (CT plus RT groups) revealed significant differences for several clinical and pathological variables, including preoperative CT ($p = 0.002$), age ($p < 0.001$), stage ($p = 0.028$), number of risk factors ($p = 0.023$), differentiation ($p = 0.007$), cell type ($p = 0.017$), and tumor size ($p < 0.001$). The number of non-preoperative CT, age < 40 years, stage IB1, fewer risk factors, high–intermediate differentiation, tumor size < 4 cm in the observation group were significantly higher than that in the adjuvant therapy group. However, the number of SCC cases in the adjuvant therapy group was significantly higher than that in the observation group. The number of DSI and LVSI between the observation group and adjuvant therapy group was not significantly different. The patient characteristics are listed in **Table 1**.

Of the 103 patients who received adjuvant therapy, 73 received CT and 30 were treated with RT. The characteristics of these patients are listed in **Table 2**. Comparison of the CT group with the adjuvant therapy group revealed no significant differences for several clinical and pathological variables, including preoperative CT ($p = 0.116$), age ($p = 0.055$), stage ($p = 0.055$), number of risk factors ($p = 0.302$), differentiation ($p = 0.246$), tumor size ($p < 0.001$), and DSI ($p = 0.886$). The number of LVSI ($p = 0.024$) and tumor size > 4 cm ($p < 0.001$) of the CT group were significantly higher than that in the RT group.

3.2. Treatment Outcome

None of the 16 patients in the observation group relapsed. There were eight cases of recurrence (seven received CT and one received RT) in the adjuvant therapy group; these patients all died of cervical cancer (**Table 1**, **Figure 1**, **Figure 2**). The outcomes of the different therapies are listed in **Table 3**. Kaplan-Meier analysis determined that the 3- and 5-year overall survival (OS) rates of the RT group were both 100% in the observation group and 94.4% and 92.3%, respectively in the adjuvant therapy group (**Table 3**, **Figure 1**); the difference was not statistically significant ($p = 0.233$).

Seven of the 73 patients died of cervical cancer in the CT group and one of the 30 patients died in the RT group. The 3- and 5-year OS rates were 93.6% and 80.7%, respectively, in the CT group and 96.4% and 96.4%, respectively, in the RT group (**Table 3**, **Figure 2**); the difference was not statistically significant ($p = 0.182$).

3.3. Prognostic Factors

We assessed the various factors for disease recurrence and death with Kaplan-Meier method and Cox regression model. We found no independent prognostic factors. The difference between the 3- and 5-year OS rates was not significant among the following factors: whether preoperative chemotherapy was received, age, stage, number of risk factors, differentiation, cell type, tumor size, type of therapy, whether adjuvant therapy was received, and whether CT or RT was received.

4. Discussion

There is no agreement among researchers regarding the classification of risk factors, and risk factors have not been classified in the NCCN Clinical Practice Guidelines or Staging Classifications and FIGO clinical practice guidelines for gynecological cancers. It is generally acknowledged that LVSI, tumor size ≥ 4 cm, and deep cervical stromal invasion are intermediate-risk factors [2]-[4]. Pelvic lymph node metastasis, positive resection

Table 1. Patient characteristics of the observation and adjuvant therapy groups.

Variables	Observation group (n, %)		Adjuvant therapy group (n, %)		$\chi 2$	p value
Preoperative CT						
No	12	75.0%	57	55.3%	38.71	0.002
Yes	4	25.0%	46	44.7%		
Age						
<40 years	12	75.0%	34	33.0%	35.51	<0.001
≥40 years	4	25.0%	69	67.0%		
Stage						
IB1	8	50.0%	39	37.9%	8.58	0.028
IB2	5	31.3%	33	32.0%		
IIA	2	12.5%	11	10.7%		
IIB	1	6.3%	20	19.4%		
Number of risk factors						
1	15	93.8%	85	82.5%	7.54	0.023
2	1	6.3%	15	14.6%		
≥3	0	0.0%	3	2.9%		
Differentiation						
Well	3	18.8%	11	10.7%	7.56	0.007
Intermediate	10	62.5%	56	54.4%		
Poor	3	18.8%	36	35.0%		
Cell type						
Squamous	12	75.0%	88	85.4%	8.19	0.017
Glandular	4	25.0%	12	11.7%		
Others	0	0.0%	3	2.9%		
Tumor size						
≤4cm	15	93.8%	55	53.4%	43.15	<0.001
>4cm	1	6.3%	48	46.6%		
Stromal invasion						
Inner half	8	50.0%	44	42.7%	0.99	0.321
Outer half	8	50.0%	59	57.2%		
LVSI						
No	14	87.5%	88	85.4%	0.19	0.408
Yes	2	12.5%	15	14.6%		

Table 2. Patient characteristics of the CT and RT groups.

Variables	RT group (n, %)		CT group (n, %)		$\chi 2$	p value
Preoperative CT						
No	19	63.3%	38	52.1%	2.48	0.116
Yes	11	36.7%	35	47.9%		
Age						
<40 years	13	43.3%	21	28.8%	3.67	0.055
≥40 years	17	56.7%	52	71.2%		
Stage						
IB1	13	43.3%	26	35.6%	3.60	0.308
IB2	7	23.3%	26	35.6%		
IIA	2	6.7%	9	12.3%		
IIB	8	26.7%	12	16.4%		
Number of risk factors						
1	23	76.7%	62	84.9%	2.40	0.302
2	6	20.0%	9	12.3%		
≥3	1	3.3%	2	2.7%		
Differentiation						
Well	3	10.0%	8	11.0%	2.81	0.246
Intermediate	14	46.7%	42	57.5%		
Poor	13	43.3%	23	31.5%		
Cell type						
Squamous	29	96.7%	59	80.8%	13.44	0.02
Glandular	1	3.3%	11	15.1%		
Others	0	0.0%	3	4.1%		
Tumor size						
≤4cm	18	60.0%	37	50.7%	0.16	0.563
>4cm	12	40.0%	36	49.3%		
DSI						
Inner half	13	43%	31	42%	0.02	0.886
Outer half	17	57%	42	58%		
LVSI						
No	23	76.7%	65	89.0%	5.10	0.024
Yes	7	23.3%	8	11.0%		

Table 3. OS between different groups.

Group	Number	Deaths	3-year OS	5-year OS	p
Observation	16	0	100.0%	100%	0.233
Adjuvant therapy	103	8	94.4%	92.3%	
CT	73	7	93.6%	80.7%	0.182
RT	30	1	96.4%	96.4%	

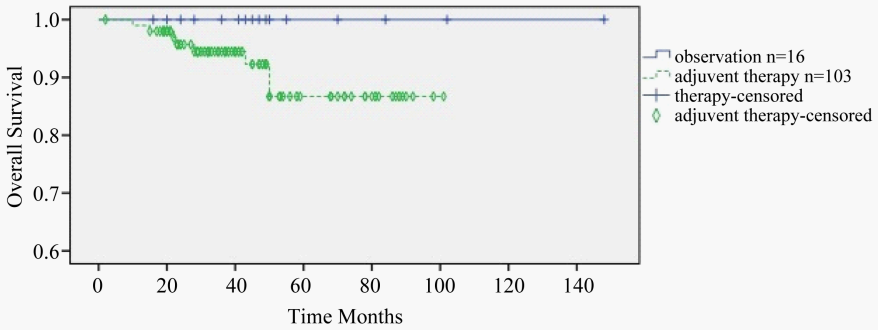

Figure 1. OS curves of observation group and adjuvant therapy group.

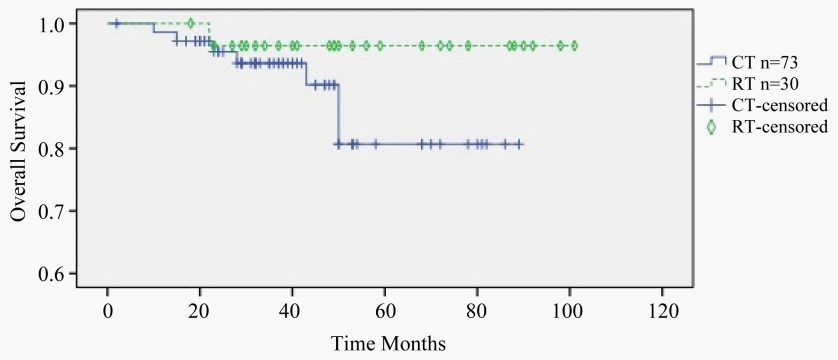

Figure 2. OS curves of CT group and RT group.

margin, and parametrial invasion are all considered as high-risk factors. The risk of recurrence after radical surgery is increased with the presence of positive lymph nodes, positive parametria, or positive surgical margins, adjuvant pelvic RT and concurrent cisplatin-containing chemotherapy improves survival compared with pelvic irradiation alone in such patients. Risk is also increased in those with uninvolved nodes but with large tumor volume, capillary-like space involvement, and invasion of the outer one-third of the cervical stroma (FIGO), or deep stromal invasion (NCCN). Adjuvant whole pelvic irradiation reduces the local failure rate and improves progression-free survival compared with treatment by surgery alone. RT appears to be particularly beneficial for patients with adenocarcinoma or adenosquamous histologies. Stage IA-IB patients with negative pelvic lymph nodes may choose pelvic RT if there is a combination of high-risk factors such as large primary tumor, DSI, and/or LVSI. However, according to NCCN guidelines, observation may also be considered for these patients, and this presents the possibility of searching for new therapeutic approaches.

Radical hysterectomy and radical RT for invasive cervical cancer are performed with the intent of curing the patient. Based on the findings of a prospective study [5], adjuvant concurrent CRT has been accepted as standard treatment for patients with high-risk factors such as parametrial extension, lymph node metastases, or positive resection margin. Adjuvant pelvic radiation alone might decrease the incidence of pelvic recurrences but not expected to prevent the development of distant metastases, which resulted in uncertain long-term survival benefits. However, these treatments can be associated with significant morbidity. Radiation can result in severe radiation cystitis, radiation rectitis, and even urinary or fecal fistula. Patients who receive CT and/or ovarian radiation are at risk of premature ovarian failure; the risk increases with increasing radiation dose. These side effects can reduce the quality of life of cancer survivors. As survival is limited by distant site recurrence, several studies have evaluated the effectiveness of adjuvant CT alone in patients with high-risk factors after radical surgery in early-stage cervical cancer [6]-[9]. The results of these studies have suggested that adjuvant CT alone is effective for local as well as distant control. Thus, the therapeutic outcome of adjuvant CT in patients with intermediate-risk factors after radical surgery in early-stage cervical cancer is worth studying.

There are only a few reports on the effectiveness of adjuvant CT in patients with intermediate-risk factors after radical surgery in cervical cancer. Masayoshi *et al*. [10] analyzed the data of 50 patients with cervical SCC who underwent radical hysterectomy and pelvic lymphadenectomy. Patients with recurrent risk factors, includ-

ing DSI, LVSI, parametrial invasion, and bulky tumor (≥4 cm), received adjuvant therapy (23 RT, 27 CT). The 3-year disease-free survival (DFS) rate was 82.6% with RT and 96.3% with CT (p = 0.16). Postoperative bowel obstruction was significantly more frequent in the RT group compared to the CT (p = 0.007) and observation groups (p = 0.0026). Urinary disturbance was also more frequent in the RT group than in the CT (p = 0.0016) and observation groups (p = 0.089). The effect of CT on DFS was no worse than that of RT for patients without multiple lymph node metastasis and was associated with fewer bowel complications. CT has equivalent therapeutic effect as RT and fewer postoperative complications for patients with intermediate-risk factors. Lee *et al*. [11] studied the outcome of CT or RT as adjuvant therapy for patients with FIGO stage IB-IIA cervical cancer and surgically confirmed intermediate-risk factors. Data were collected from patients who received adjuvant chemotherapy following radical hysterectomy with pelvic lymph node dissection (RHLND, cases, n = 38) or adjuvant RT following RHLND (controls, n = 40). Adjuvant treatment was administered to patients with a combination of intermediate-risk factors, including DSI (>50%), LVSI, large tumor size (3 - 6 cm), or close vaginal resection margin (<1 cm). The difference in DFS rates was not significant (p = 0.68). However, analysis of the OS was incomplete due to the limited number of events available at the end of the study period. The findings of this study suggested that adjuvant CT might be effective in patients with FIGO stage IB-IIA uterine cervical cancer and surgically confirmed intermediate-risk factors. Nobuhiro *et al*. [9] studied the effectiveness of CT alone as postoperative adjuvant therapy for intermediate- and high-risk cervical cancer. The study group comprised 65 consecutive patients with stage IB or IIA squamous cell or adenosquamous cervical cancer. Tumors were intermediate risk (DSI, n = 30) or high risk (positive surgical margin, parametrial invasion, and/or lymph node involvement, n = 35). The estimated 5-year DFS was 93.3% for the 30 patients with intermediate-risk tumors (SCC: 100%; adenosquamous carcinoma: 71.4%) and 85.7% for the 35 patients with high-risk tumors (SCC: 89.3%; adenosquamous carcinoma: 71.4%). The incidence of regional recurrence was 3.3% in the intermediate-risk group and 8.6% in the high-risk group. The results suggested the potential role of adjuvant CT alone for patients with cervical cancer. According to the NCCN guidelines, observation may also be considered for patients with intermediate-risk cervical cancer after surgery.

In our study, statistically significant differences were not found for the 3- or 5-year OS rates of the observation and adjuvant therapy groups (3-year OS: 100% and 94.4%, respectively; 5-year OS: 100% and 92.3%, respectively). Statistically significant differences were also not found in the 3- or 5-year OS rates of the CT and RT groups (3-year OS: 93.6% and 96.4%, respectively; 5-year OS: 80.7% and 96.4%, respectively). We calculated the OS using the Kaplan-Meier method, and the difference was not statistically significant among all of the variables. Therefore, the difference of the characters did not affect the OS between different groups, especially between the CT group and RT group. Our results suggest the potential role of adjuvant CT alone for intermediate-risk patients with cervical cancer after surgery, especially those who are younger, with well-differentiated disease, or are at the early stage. Therefore, we believe that a prospective randomized trial of CT versus RT as optional adjuvant therapy for patients with intermediate-risk factors for recurrence is worthwhile.

Factors such as stage, cell type, differentiation, age, bulky tumor (>4 cm), LVSI, DSI, positive lymph nodes, positive parametria, and positive surgical margins were considered as risk factors for cervical cancer. Multivariate analyses showed that there were no independent prognostic factors in our study. This conclusion might be attributed to homogeneity, as all patients in our cohort were intermediate risk and we analyzed only 119 cases. A conclusion regarding prognostic factors might be drawn if data were obtained from high-risk patients and risk-free patients.

References

[1] Nam, J.H., Park, J.Y., Kim, D.Y., *et al*. (2012) Laparoscopic versus Open Radical Hysterectomy in Early-Stage Cervical Cancer: Long-Term Survival Outcomes in a Matched Cohort Study. *Annals of Oncology*, **23**, 903-911. http://dx.doi.org/10.1093/annonc/mdr360

[2] Park, J.Y., Kim, D.Y., Kim, J.H., *et al*. (2011) Outcomes after Radical Hysterectomy According to Tumor Size Divided by 2-cm Interval in Patients with Early Cervical Cancer. *Annals of Oncology*, **22**, 59-67. http://dx.doi.org/10.1093/annonc/mdq321

[3] Song, S., Song, C., Kim, H.J., *et al.* (2012) 20-Year Experience of Postoperative Radiotherapy in IB-IIA Cervical Cancer Patients with Intermediate Risk Factors: Impact of Treatment Period and Concurrent Chemotherapy. *Gynecologic Oncology*, **124**, 63-67. http://dx.doi.org/10.1016/j.ygyno.2011.09.033

[4] Garg, G., Shah, J.P., Toy, E.P., *et al*. (2011) Stage IIA1 versus Stage IIA2 Cervical Cancer: Does the New Staging

Criteria Predict Survival? *International Journal of Gynecological Cancer*, **21**, 711-716. http://dx.doi.org/10.1097/IGC.0b013e3182138648

[5] Peters, W.A., Liu, P.Y., Barrett, R.J., *et al*. (2000) 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. *Journal of Clinical Oncology*, **18**, 1606-1613. http://dx.doi.org/10.1097/00006254-200008000-00017

[6] Lahousen, M., Haas, J., Pickel, H., *et al*. (1999) Chemotherapy versus Radiotherapy versus Observation for High-Risk Cervical Carcinoma after Radical Hysterectomy: A Randomized, Prospective, Multicenter Trial. *Gynecologic Oncology*, **73**, 196-201. http://dx.doi.org/10.1006/gyno.1999.5343

[7] Curtin, J.P., Hoskins, W.J., Venkatraman, E.S., *et al*. (1996) Adjuvant Chemotherapy versus Chemotherapy plus Pelvic Irradiation for High-Risk Cervical Cancer Patients after Radical Hysterectomy and Pelvic Lymphadenectomy (RH-PLND): A Randomized Phase III Trial. *Gynecologic Oncology*, **61**, 3-10. http://dx.doi.org/10.1006/gyno.1996.0087

[8] Iwasaka, T., Kamura, T., Yokoyama, M., *et al*. (1998) Adjuvant Chemotherapy after Radical Hysterectomy for Cervical Carcinoma: A Comparison with Effects of Adjuvant Radiotherapy. *Obstetrics & Gynecology*, **91**, 977-981. http://dx.doi.org/10.1016/S0029-7844(98)00079-9

[9] Takeshima, N., Umayahara, K., Fujiwara, K., *et al*. (2006) Treatment Results of Adjuvant Chemotherapy after Radical Hysterectomy for Intermediate- and High-Risk Stage IB-IIA Cervical Cancer. *Gynecologic Oncology*, **103**, 618-622. http://dx.doi.org/10.1016/j.ygyno.2006.04.019

[10] Hosaka, M., Watari, H., Takeda, M., *et al*. (2008) Treatment of Cervical Cancer with Adjuvant Chemotherapy versus Adjuvant Radiotherapy after Radical Hysterectomy and Systematic Lymphadenectomy. *The Journal of Obstetrics and Gynaecology Research*, **34**, 552-556. http://dx.doi.org/10.1111/j.1447-0756.2008.00739.x

[11] Lee, K.B., Lee, J.M., Ki, K.D., *et al.* (2008) Comparison of Adjuvant Chemotherapy and Radiation in Patients with Intermediate Risk Factors after Radical Surgery in FIGO Stage IB-IIA Cervical Cancer. *International Journal of Gynecological Cancer*, **18**, 1027-1031. http://dx.doi.org/10.1111/j.1525-1438.2007.01136.x