

Comparison of chemoradiotherapy with and without brachytherapy as adjuvant therapy after radical surgery in early-stage cervical cancer with poor prognostic factors

An observational study

Mei-Ling Lan, MS, Xian Yu, MD, He Xiao, MS, Peng Zhou, MD, Nan Hu, MD, PhD, Yun Liu, MS, Ge Wang, MD, PhD*

Abstract

This study aimed to determine whether the addition of intracavitary brachytherapy (ICBT) to chemoradiotherapy (CRT) improves outcome in patients with cervical cancer and poor prognostic factors. Patients with stage IB to IIA cervical cancer who had undergone radical hysterectomy and pelvic lymphadenectomy between August 2008 and December 2014 were retrospectively registered in this study. All patients received external beam radiation therapy (EBRT) + chemotherapy, and some patients additionally received ICBT. EBRT consisted of 45 to 50.4 Gy delivered to the standard pelvic field in 25 to 28 fractions. Chemotherapy consisted of 2 to 4 courses of weekly cisplatin-based treatment. ICBT was delivered in 1 to 3 insertions. Ninety-seven of 163 patients received CRT, and 66 patients additionally received ICBT. During a median follow-up period of 33 months, recurrence was detected in 38 patients. The 3-year locoregional control (LRC), disease-free survival (DFS), and overall survival (OS) rates did not differ significantly between patients who did and did not receive ICBT. In subgroup analyses, fewer recurrences were seen in patients with at least 1 high-risk factor who received ICBT than in those who did not, with a significant (62%) reduction in the risk of progression or death (hazard ratio 0.384, 95% confidence interval 0.151–0.978, $P=.045$). The difference in OS between the CRT and CRT+ICBT subgroups was marginal ($P=.064$). The addition of ICBT to CRT after radical surgery significantly improves LRC and DFS rates in women with cervical cancer and at least 1 high-risk factor.

Abbreviations: CI = confidence interval, CRT = chemoradiotherapy, CT = chemotherapy, DFS = disease-free survival, EBRT = external beam radiation therapy, FIGO = International Federation of Gynecology and Obstetrics, HR = hazard ratio, ICBT = intracavitary brachytherapy, LRC = locoregional control, LVSI = lymphovascular space involvement, OS = overall survival, PFS = progression-free survival, PLN = pelvic lymph node, RT = radiotherapy.

Keywords: brachytherapy, cervical cancer, radiotherapy, survival

Editor: Laszlo Geza Boros.

M-LL and XY contributed equally to this work.

Author contributions: M-LL performed the study, managed the literature searches and analyses, and wrote the first draft of the manuscript. XY conceived and designed the research. HX performed the statistical analysis. PZ, YL, and NH collected the data. GW critically reviewed the intellectual content and gave final approval of the version to be submitted. All authors read and approved the final manuscript.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

Cancer Center, Institute of Surgical Research, Daping Hospital, The Military Medical University, Chongqing, China.

* Correspondence: Ge Wang, Cancer Center, Institute of Surgical Research, Daping Hospital, The Military Medical University, No. 10 Changjiang Zhilu, Yuzhong District, Chongqing 400042, China (e-mail: wangge70@hotmail.com).

Copyright © 2017 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2017) 96:46(e8384)

Received: 10 February 2017 / Received in final form: 8 September 2017 /

Accepted: 26 September 2017

<http://dx.doi.org/10.1097/MD.0000000000008384>

1. Introduction

Cervical cancer is the third most common malignancy and the fourth leading cause of malignancy-related death in women worldwide.^[1] The majority (>85%) of cervical cancer cases occur in developing countries, where the disease is a major cause of morbidity and mortality.^[2] Primary therapies for early-stage cervical cancer include surgery and radiotherapy (RT). These 2 methods are associated with similar disease-free survival (DFS) and overall survival (OS) rates in patients with early-stage disease,^[3–5] but patients tend to prefer surgery as the primary mode of treatment.^[6]

Depending on disease stage and intraoperative findings, adjuvant therapy may be indicated for women who have undergone radical hysterectomy due to the presence of intermediate or high pathologic risk factors. Intermediate risk in such patients is classified based on a combination of the following factors: lymphovascular space involvement (LVSI), deep stromal invasion, and tumor diameter.^[7] Tumor histology may also be considered in the determination of intermediate risk.^[8] Positive pelvic lymph nodes (PLNs), parametrial involvement, and positive resection margins are considered as high risk.^[9] Numerous studies have shown that postoperative adjuvant chemoradiotherapy (CRT) can improve outcomes in

patients with intermediate-risk factors.^[10–13] For high-risk patients with early-stage cervical cancer who have undergone radical hysterectomy with pelvic lymphadenectomy, postoperative pelvic RT with concurrent cisplatin chemotherapy (CT) can also improve progression-free survival (PFS) and OS.^[9] However, there are still a considerable number of patients who relapse after these comprehensive treatments.

Recurrence is much more common in patients with positive resection margins, parametrial involvement, PLN metastasis, LVSI, and deep stromal invasion, and is affected by tumor diameter and histologic type.^[14–19] As a result, some institutions have added brachytherapy to CRT (CT+pelvic RT) to boost the radiation dose to the primary tumor and improve disease control and survival.^[20] In our institution, the general criteria used to determine indication for ICBT treatment are at least 2 intermediate-risk factors or at least 1 high-risk factor. However, other institutions have hesitated to use CRT in combination with intracavitary brachytherapy (ICBT) for patients with poor prognostic factors who have undergone radical surgery, due to concern about adverse acute and/or chronic vaginal effects of ICBT (eg, cystitis, proctitis, vaginal contracture), and because patients with early-stage cervical cancer tend to have favorable prognoses. Hence, physicians' determination of whether brachytherapy should be added to CRT is crucial to avoid overtreatment. Therefore, it is highly critical that researchers explore and verify clinicopathologic characteristics, even a molecular signature, as predictors of a good clinical response to ICBT. Some have suggested that patients with at least 1 high-risk factor can benefit from ICBT, but not those with 1 to 2 intermediate-risk factors, including deep stromal invasion, LVSI, tumor diameters ≥ 4 cm, and low differentiation.^[20,21] We thus undertook this study to explore whether the addition of adjuvant vaginal brachytherapy to CRT after primary radical hysterectomy could improve locoregional control (LRC), DFS, and OS in patients with at least 1 high-risk factor.

2. Methods

2.1. Patients

This single-center retrospective study involved patients with International Federation of Gynecology and Obstetrics (FIGO) stage IB to IIA cervical cancer who underwent radical hysterectomy and PLN dissection between August 2008 and December 2014. All patients received postoperative RT and CT. Patients included in the study had at least 1 high-risk factor (parametrial involvement, positive or close resection margins, PLN metastasis) or at least 2 intermediate-risk factors (deep stromal invasion, LVSI, tumor diameter ≥ 4 cm, nonsquamous carcinoma histology). The study received institutional review board approval, and all patients provided written informed consent.

Patients were divided into 2 groups according to recommended treatment: patients in group A received adjuvant external beam radiation therapy (EBRT) and cisplatin-based CT, and those in group B additionally received ICBT. Patients who showed recurrence after radical hysterectomy and before receipt of EBRT were excluded from this study.

2.2. Adjuvant therapy

External beam radiation therapy (1.8–2 Gy/d, days 1–5 of each week) was delivered with an 8-MV x-ray (CMS XIO 6.0; Elekta

Synergy Systems, Stockholm, Sweden) by 3-dimensional conformal RT or intensity-modulated RT. The median dose delivered to the whole pelvic region was 50 (range 45–50.4) Gy, in 25 to 28 fractions. EBRT normally started within 3 months after surgery. At the end of the EBRT course, some patients received iridium-192 high-dose-rate brachytherapy by remote control after loading system. A vaginal cylinder was used for cuff brachytherapy, and the upper 3 cm of the vagina was treated with the dose prescribed at 0.5 cm from the cylinder surface. The dose was 6 to 10 Gy/wk. Californium-252 neutron ICBT was delivered at a rate of 11 to 12 Gy/wk to the remaining patients. The median doses of iridium-192 and californium-252 neutron ICBT were 16 (range 10–20) Gy and 23 (range 22–24) Gy, respectively. Both were administered once a week in 1 to 3 insertions. CT consisted of 2 to 4 cycles of weekly cisplatin or cisplatin-based treatment, as part of concurrent and/or sequential chemoradiotherapy, for all patients.

2.3. Follow-up

After treatment completion, patients were followed at 3-monthly intervals for the first 2 years, 6-monthly intervals for an additional 3 to 5 years, and then annually. At each follow-up visit, a complete medical history was obtained, and physical examination, cytology, laboratory studies, and imaging were performed. Patients were assessed throughout treatment and for 90 days after its completion to monitor for acute cystitis and proctitis toxicity. Any effect that occurred ≥ 90 days from the start of treatment was considered to represent late toxicity, based on the Radiation Therapy Oncology Group scale.

2.4. Outcomes

Overall survival and DFS were defined as the time from surgery to death from any cause and to first disease recurrence/death, respectively. LRC was defined as the absence of recurrence in the vaginal/pelvic region, with censoring for loss to follow-up or death from any other cause.

2.5. Statistical analysis

The chi-square test was used to study associations between ICBT-treated/nontreated subgroups and clinicopathologic characteristics. The nonparametric Kruskal–Wallis test was used to evaluate differences in continuous variables between these subgroups. LRC, DFS, and OS were calculated by the Kaplan–Meier method, and the log-rank test was used to assess differences between groups. To test whether ICBT effects were confounded in subgroup analysis, multivariate Cox proportional-hazards regression models with forward stepwise selection ($P_E < .05$ for entry and $P_R > .10$ for backward elimination) were applied to identify prognostic factors among all baseline characteristics and ICBT, which were treated as categorical variables, except for risk factor numbers, which were treated as continuous variables.^[22,23] To identify patients who would benefit from ICBT, the entire sample was stratified by high-risk factors, and Cox multivariate regressions were used to test the interactions between treatments (with and without ICBT), and subgroups adjusted for other relevant clinical covariates including age, stage, tumor diameter, histology, pelvic nodal metastasis, interstitial infiltration, chemotherapy regimen, chemotherapy cycle, and radiotherapy manner and so on. The chi-square test and Fisher exact probability method were used to evaluate the association between toxicity and brachytherapy. P values $< .05$ were defined as

statistically significant. Statistical analyses were performed using SPSS software (version 16.0; SPSS Inc., Chicago, IL).

2.6. Ethical approval and consent to participate

The experimental protocol was established according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of the Cancer Center, Institute of Surgical Research, Daping Hospital, The Military Medical University, Chongqing, China. All patients or guardians completed and signed consent forms indicating their agreement to study participation.

3. Results

3.1. Patients

Table 1 shows the characteristics of the 163 patients (group A, n=97; group B, n=66) included in the study. The median age was 44 (range 26–73) years. Twenty-three patients had FIGO stage IB1 disease, 30 had stage IB2, 56 had stage IIA1, and 54 had stage IIA2 disease. All patients with positive resection margins received ICBT. Twenty-eight patients were treated with iridium-192 and 38 were treated with californium-252. The groups were well-matched with respect to commonly defined clinicopathologic characteristics.

3.2. Failure patterns

During a median follow-up period of 33 (range 6–99) months, recurrence was detected in 26 (26.8%) patients in group A and 12 (18.2%) patients in group B. In group A, recurrence was locoregional (n=5, 5.2%), in distant areas outside of the pelvis (n=14, 14.4%), and in locoregional and distant areas (n=7, 7.2%). In group B, these forms of recurrence were detected in 2 (3.0%), 8 (12.1%), and 2 (3.0%) cases, respectively. During the follow-up period, 16 patients in group A and 7 patients in group B died of cervical cancer. Recurrence sites are summarized in Table S1 (<http://links.lww.com/MD/B946>).

3.3. Survival outcomes

Kaplan–Meier analysis showed no significant difference in 3-year LRC, DFS, or OS between groups. These rates were 84.9%, 72.2%, and 81.7%, respectively, in group A, and 93.8%, 79.8%, and 89.7%, respectively, in group B (Fig. 1). Univariate analysis showed that the most important factors influencing DFS were PLN metastasis and parametrial involvement. Patients with these 2 factors had worse prognoses (hazard ratio [HR] 1.932, $P=.047$; and HR 2.311, $P=.030$, respectively). In addition, OS was significantly poorer in patients with than in those without nonsquamous cell histology (HR 2.629, $P=.043$; Table S2, <http://links.lww.com/MD/B946>).

Multivariate analysis revealed that histology, tumor diameter, and PLN metastasis were unfavorable prognostic factors for LRC. Parametrial involvement and histology were the only significant risk factors for DFS and OS, respectively (Table S3, <http://links.lww.com/MD/B946>).

3.4. Results of subgroup analysis

Subgroup analyses showed that patients with 2 or more intermediate-risk factors, but no high-risk factor, did not benefit from ICBT. LRC, DFS, and OS were similar between subgroups of these patients who did and did not receive ICBT. However, LRC and DFS periods

were significantly longer in patients with at least 1 high-risk factor who received CRT+ICBT than in those who received adjuvant CRT alone (log-rank test, $P=.048$ and $P=.037$, respectively). In addition, the OS was slightly higher in the CRT+ICBT group than in the CRT-only group, although this difference was not significant ($P=.064$; Fig. 2). Correspondingly, Cox regression analysis showed reductions in the risks of locoregional recurrence (HR 0.240, 95% confidence interval [CI] 0.052–1.113, $P=.068$) and progression or death (HR 0.384, 95% CI 0.151–0.978, $P=.045$; HR 0.318, 95% CI 0.089–1.139, $P=.078$) in the ICBT group.

Furthermore, in the subgroup with at least 1 high-risk factor, the Cox regression analysis with forward stepwise selection showed that after adjustment for relevant clinical covariates (ie,

Table 1
Baseline characteristics between 2 groups.

	N	Brachytherapy		P
		Nontreated	Treated	
Age, y				
≤45	94	60	34	.129
>45	69	37	32	
Stage				
IB1–IB2	53	34	19	.402
IIA1–IIA2	110	63	47	
Histology				
Squamous	138	79	59	.167
Others	25	18	7	
Tumor diameter, cm				
<4	57	36	21	.486
≥4	106	61	45	
PLN metastasis				
No	89	52	37	.758
Yes	74	45	29	
Deep stromal invasion				
<1/2	11	5	6	.355
≥1/2	152	92	60	
LVSI				
No	111	63	48	.296
Yes	52	34	18	
Parametrial involvement				
No	138	85	53	.203
Yes	25	12	13	
Type of surgery				
Laparoscope	143	85	58	.962
Abdominal cavity	20	12	8	
Positive resection margin				
No	152	97	55	<.001
Yes	11	0	11	
Radiotherapy manner				
3DCRT	143	77	66	<.001
IMRT	20	20	0	
Chemotherapy regimen				
Cisplatin alone	33	9	24	<.001
Cisplatin-based	130	88	42	
		Median (range)	Median (range)	
Tumor diameter		4 (1.00–7.50)	4.5 (2.00–7.00)	.166
Invasive nodal number		0 (0–22)	0 (0–8)	.499
Radiotherapy dose		50 (45–50.4)	50 (45–50)	<.001
Chemotherapy cycle		2 (2–4)	3 (2–4)	.024
Middle risk number		2 (1–4)	2 (0–3)	.549
High risk number		1 (0–2)	1 (0–2)	.210
Any risk number		2 (2–6)	3 (1–5)	.808

3DCRT=3-dimensional conformal radiotherapy, IMRT=intensity-modulated radiotherapy, LVSI=lymphovascular space involvement, PLNs=pelvic lymph nodes.

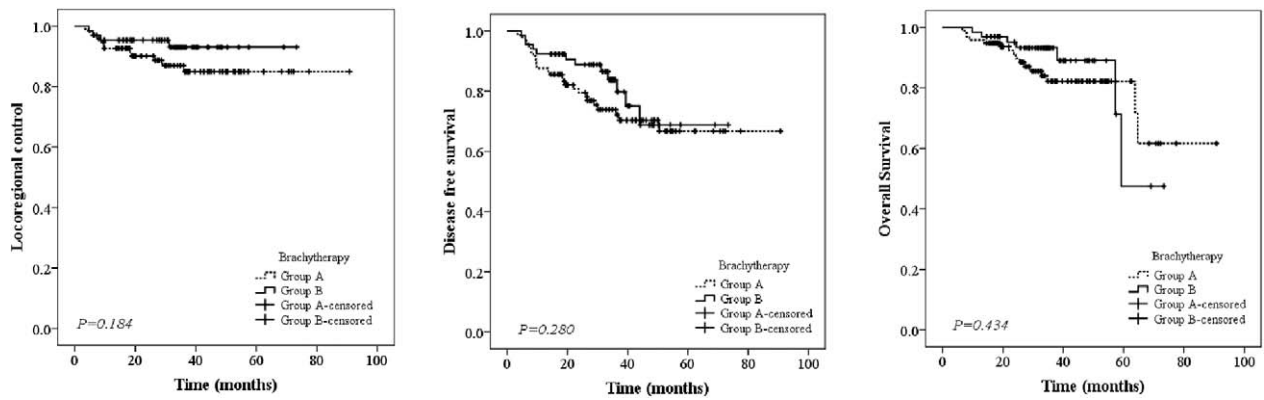


Figure 1. Locoregional control, disease-free survival, and overall survival in patients treated with and without brachytherapy. Group A, radiochemotherapy alone; group B, radiochemotherapy plus brachytherapy.

age, stage, tumor diameter, histology, pelvic nodal metastasis, interstitial infiltration, chemotherapy regimen, chemotherapy cycle, and radiotherapy manner, and so on), the number of intermediate risk factors and ICBT remained the only independent prognostic factors for LRC and DFS (Table 2).

However, for the whole population, a Cox multivariate regression model including all of the above clinical covariates, ICBT, high-risk factors (as binary covariates), and the interaction between ICBT and high-risk factors showed that this interaction had a significant effect on OS ($P_{\text{interaction}} = .022$), and had a borderline significance for DFS ($P_{\text{interaction}} = .094$). The impact of status of high-risk factors on benefits from ICBT with respect to

LRC was not evaluated in this study because there was not a convergency of coefficients in the Cox regression.

3.5. Complications

The incidence of complications is shown in Table 3. Less acute cystitis and proctitis toxicity was observed in group A than in group B ($P = .006$ and $P = .002$, respectively). Grade 3 or 4 acute adverse effects were noted in 3 patients in group A (2 cystitis and 1 proctitis) and 4 patients in group B (1 cystitis and 3 proctitis). However, the occurrence of chronic cystitis and proctitis toxicity was similar in the 2 groups. Two patients (1 in group A, 1 in

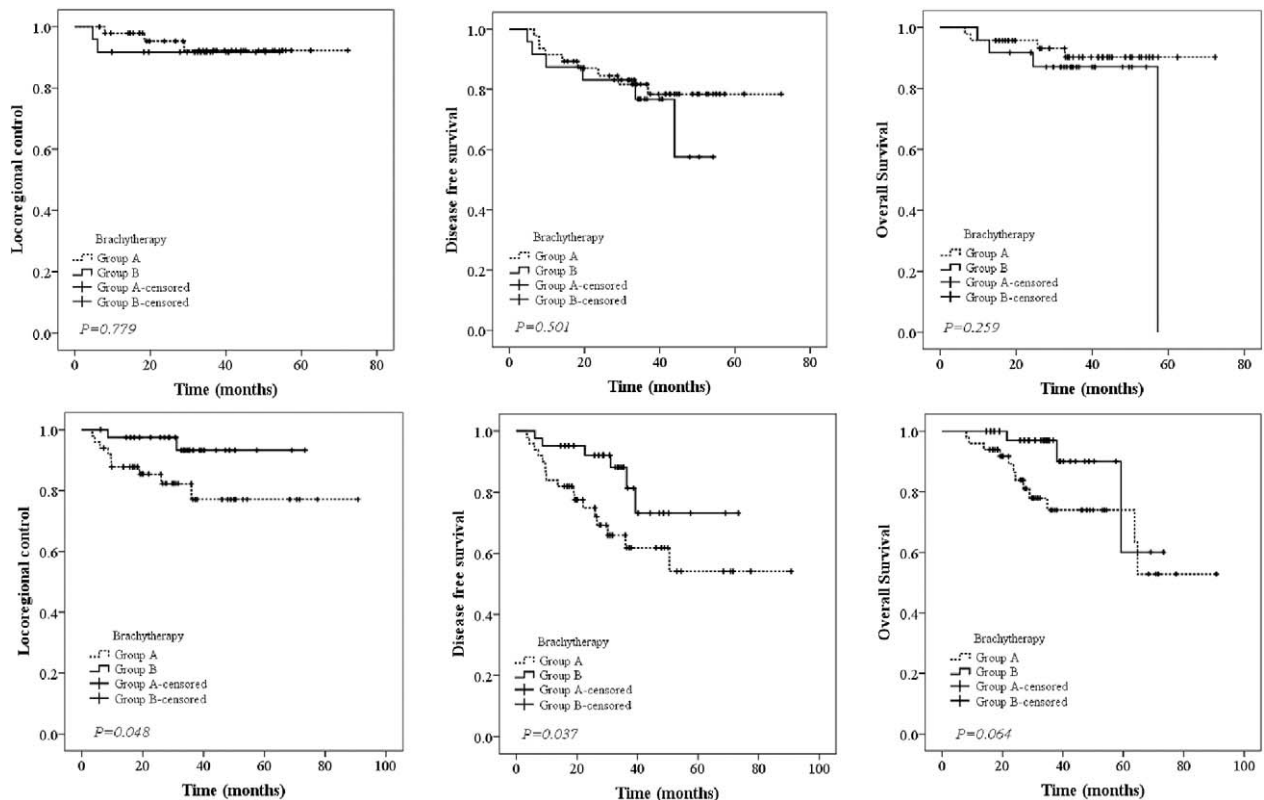


Figure 2. Clear benefit of brachytherapy added to radiochemotherapy in patients with at least 1 high-risk factor. Upper panels, patients with no high-risk factor; lower panels, patients with at least 1 high-risk factor. Group A, radiochemotherapy alone; group B, radiochemotherapy plus brachytherapy.

Table 2**Forward stepwise Cox regression based on likelihood ratio test in 92 patients' subset.**

	Clinical factors	β	SE	Wald	P	HR	95.0% CI for Exp (B)	
							Lower	Upper
LRC	Brachytherapy (yes vs no)	-1.498	0.787	3.621	.057	0.224	0.048	1.046
	Number of middle risk*	1.063	0.434	5.995	.014	2.895	1.236	6.781
DFS	Brachytherapy (yes vs no)	-1.032	0.478	4.655	.031	0.356	0.140	0.910
	Number of middle risk*	0.686	0.301	5.208	.022	1.986	1.102	3.580

CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, LRC = locoregional control.

* As continuous variable entered equation.

group B) had chronic grade 3 or 4 cystitis and proctitis toxicity. All grade 3 to 4 cystitis and proctitis toxicity were transient and tolerable with supportive treatment. No treatment-related death was reported in this cohort.

4. Discussion

This study showed that postoperative adjuvant CRT+ICBT increases LRC and DFS in patients with early-stage cervical cancer and at least 1 high-risk factor. They also suggest that patients with no high-risk factor and 2 or more intermediate-risk factors did not benefit from ICBT.

Although brachytherapy (ICBT and interstitial brachytherapy) has been an indispensable component of the successful treatment of locally advanced stage IB2 to IVA cervical cancer for more than 100 years, many physicians remain reluctant to administer postoperative ICBT to patients with poor prognostic factors for several reasons. First, radical hysterectomy with PLN dissection results in the removal of the primary cervical tumor. Second, brachytherapy is invasive, resource intensive, and can be applied only to patients with good performance status. Third, combined modalities are more likely to result in serious complications. ICBT tends to be recommended for patients with primary cervical cancer who are not candidates for surgery.^[24,25] The use of adjuvant RT and/or CT in attempts to eradicate microscopic residual tumors is preferred in patients with high relapse risk. Although adjuvant CT reduces the recurrence rate, this rate was found to be significant in patients receiving CRT.^[9]

Although LRC, DFS, and OS did not differ significantly between groups A and B in this study, some patients in the high-

risk subgroup benefitted from ICBT. These results are consistent with those of a retrospective study, which suggests that ICBT improves outcomes in high-risk patients (at least 2 of 3 risk factors: adenocarcinoma, PLN metastasis, and parametrial involvement).^[20] However, we found no significant difference in survival rates between the CRT + ICBT and CRT subgroups among patients with no high-risk factor and at least two intermediate-risk factors. Thus, a prospective study is needed to confirm the benefit of postoperative ICBT in patients with cervical cancer according to risk factor types and combinations.

The addition of brachytherapy serves to deliver a highly effective dose to the gross tumor and has been found to improve survival.^[26,27] Han et al^[20] and Tanderup et al^[28] have thus suggested that brachytherapy is not an optional part of standard definitive treatment for locally advanced cervical cancer, although its utilization for the treatment of cervical cancer is declining in the United States. Physicians hesitate to add ICBT to CRT after radical hysterectomy, as it may enhance morbidity and increase radiation-related toxicity in patients with favorable prognoses. In our study, all acute and chronic toxicity was moderate, and no treatment-related death occurred.

Vaginal brachytherapy may be a useful boost for patients with positive surgical margins.^[29,30] Therefore, we recommend the addition of brachytherapy, which might be associated with a better survival outcome, for our patients with close or positive resection margins. This approach may explain the lack of significance of positive resection margins in the multivariate analysis.

In the present study, intermediate risk was defined using the 2 factor model (2 or more of the following: deep stromal invasion, LVSI, tumor diameter ≥ 4 cm, and nonsquamous carcinoma histology), which differs from the Gynecologic Oncology Group criteria,^[7] as we sought to determine which combination of risk factors would show a benefit from ICBT. Survival outcomes were comparable among patients in the intermediate-risk subgroup who received intracavitary treatment and those who received CRT alone. In the high-risk subgroup, vaginal cuff irradiation appeared to improve LRC and DFS; the role of additional vaginal cuff irradiation, however, remains controversial.

Limitations of this study include the retrospective design, small sample, short follow-up period, and high ratio of censored data. Further research is thus required to determine whether adjuvant brachytherapy improves survival outcomes in patients with poor prognostic factors after radical hysterectomy.

5. Conclusions

Our study demonstrated that the addition of ICBT to CRT can profoundly decrease recurrence and improve PFS in patients with

Table 3**Acute and chronic toxicity in patients who did and did not receive brachytherapy.**

Advent events and grade	N	Brachytherapy		P
		Nontreated (n=97)	Treated (n=66)	
Acute cystitis	0	82	58	.006*
	1-2	78	37	
	3-4	3	2	
Chronic cystitis	0	132	81	.306*
	1-2	30	16	
	3-4	1	0	
Acute proctitis	0	38	31	.002*
	1-2	121	65	
	3-4	4	1	
Chronic proctitis	0	130	81	.166*
	1-2	32	15	
	3-4	1	0	

* Fisher exact probability.

at least 1 high-risk factor after radical hysterectomy. Further research with longer follow-up periods and a prospective, randomized controlled study design should be conducted to evaluate the efficacy of brachytherapy as part of adjuvant treatment.

References

- [1] Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin* 2011;61:69–90.
- [2] International Agency for Research on Cancer Cervical Cancer Estimated Incidence, Mortality and Prevalence Worldwide in 2012. 2012; World Health Organization,
- [3] Hopkins MP, Morley GW. Radical hysterectomy versus radiation therapy for stage IB squamous cell cancer of the cervix. *Cancer* 1991;68:272–7.
- [4] 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.
- [5] 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;96:721–8.
- [6] Quinn MA, Benedet JL, Odicino F, et al. Carcinoma of the cervix uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet* 2006;95(suppl 1):S43–103.
- [7] Sedlis A, Bundy BN, Rotman MZ, et al. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group Study. *Gynecol Oncol* 1999;73:177–83.
- [8] Ryu SY, Kim MH, Nam BH, et al. Intermediate-risk grouping of cervical cancer patients treated with radical hysterectomy: a Korean Gynecologic Oncology Group study. *Br J Cancer* 2014;110:278–85.
- [9] Peters WA 3rd, Liu PY, Barrett 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;18:1606–13.
- [10] Ryu SY, Park SI, Nam BH, et al. Is adjuvant chemoradiotherapy overtreatment in cervical cancer patients with intermediate risk factors? *Int J Radiat Oncol Biol Phys* 2011;79:794–9.
- [11] Mabuchi S, Morishige K, Isohashi F, et al. Postoperative concurrent nedaplatin-based chemoradiotherapy improves survival in early-stage cervical cancer patients with adverse risk factors. *Gynecol Oncol* 2009;115:482–7.
- [12] Song S, Song C, Kim HJ, et al. 20 year experience of postoperative radiotherapy in IB-IIA cervical cancer patients with intermediate risk factors: impact of treatment period and concurrent chemotherapy. *Gynecol Oncol* 2012;124:63–7.
- [13] Kim K, Kang SB, Chung HH, et al. Comparison of chemoradiation with radiation as postoperative adjuvant therapy in cervical cancer patients with intermediate-risk factors. *Eur J Surg Oncol* 2009;35:192–6.
- [14] Hart K, Han I, Deppe G, et al. Postoperative radiation for cervical cancer with pathologic risk factors. *Int J Radiat Oncol Biol Phys* 1997;37:833–8.
- [15] 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;75:328–33.
- [16] Atlan D, Touboul E, Deniaud-Alexandre E, et al. Operable Stages IB and II cervical carcinomas: a retrospective study comparing preoperative uterovaginal brachytherapy and postoperative radiotherapy. *Int J Radiat Oncol Biol Phys* 2002;54:780–93.
- [17] Horn LC, Fischer U, Raptis G, et al. Tumor size is of prognostic value in surgically treated FIGO stage II cervical cancer. *Gynecol Oncol* 2007;107:310–5.
- [18] Xia X, Xu H, Wang Z, et al. Analysis of prognostic factors affecting the outcome of stage IB-IIb cervical cancer treated by radical hysterectomy and pelvic lymphadenectomy. *Am J Clin Oncol* 2016;39:604–8.
- [19] Noh JM, Park W, Kim YS, et al. Comparison of clinical outcomes of adenocarcinoma and adenosquamous carcinoma in uterine cervical cancer patients receiving surgical resection followed by radiotherapy: a multicenter retrospective study (KROG 13-10). *Gynecol Oncol* 2014;132:618–23.
- [20] Davila Fajardo R, van Os R, Buist MR, et al. Post-operative radiotherapy in patients with early stage cervical cancer. *Gynecol Oncol* 2014;134:52–9.
- [21] Yu H, Zhang LL, Du X, et al. Postoperative adjuvant chemotherapy combined with intracavitary brachytherapy in early-stage cervical cancer patients with intermediate risk factors. *Onco Targets Ther* 2016;1:7331–5.
- [22] Lu C, Soria JC, Tang X, et al. Prognostic factors in resected stage I non-small-cell lung cancer: a multivariate analysis of six molecular markers. *J Clin Oncol* 2004;22:4575–83.
- [23] van den Bent MJ, Dubbink HJ, Marie Y, et al. IDH1 and IDH2 mutations are prognostic but not predictive for outcome in anaplastic oligodendroglial tumors: a report of the European Organization for Research and Treatment of Cancer Brain Tumor Group. *Clin Cancer Res* 2010;16:1597–604.
- [24] Logsdon MD, Eifel PJ. FIGO IIIB squamous cell carcinoma of the cervix: an analysis of prognostic factors emphasizing the balance between external beam and intracavitary radiation therapy. *Int J Radiat Oncol Biol Phys* 1999;43:763–75.
- [25] Lei X, Qian CY, Qing Y, et al. Californium-252 brachytherapy combined with external-beam radiotherapy for cervical cancer: long-term treatment results. *Int J Radiat Oncol Biol Phys* 2011;81:1264–70.
- [26] Gaffney DK, Erickson-Wittmann BA, Jhingran A, et al. ACR appropriateness criteria(R) on Advanced Cervical Cancer Expert Panel on Radiation Oncology-Gynecology. *Int J Radiat Oncol Biol Phys* 2011;81:609–14.
- [27] Monk BJ, Tewari KS, Koh WJ. Multimodality therapy for locally advanced cervical carcinoma: state of the art and future directions. *J Clin Oncol* 2007;25:2952–65.
- [28] Chen MF, Tseng CJ, Tseng CC, et al. Clinical outcome in posthysterectomy cervical cancer patients treated with concurrent Cisplatin and intensity-modulated pelvic radiotherapy: comparison with conventional radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;67:1438–44.
- [29] Atkovar G, Uzel O, Ozsahin M, et al. Postoperative radiotherapy in carcinoma of the cervix: treatment results and prognostic factors. *Radiother Oncol* 1995;35:198–205.
- [30] Bandera L, La Face B, Antonioli C, et al. Survival and toxicity of radical radiotherapy (with or without brachytherapy) for FIGO stage I and II cervical cancer: a mono-institutional analysis. *Eur J Gynaecol Oncol* 2014;35:121–7.