Table 1
The incidence of ovarian metastasis

FIGO stage	Squamous cell carcinoma	Adenocarcinoma
Stage Ib	4/1784 (0.22%)	14/376 (3.72%)
Stage IIa	3/402 (0.75%)	2/38 (5.26%)
Stage IIb	16/739 (2.17%)	13/132 (9.85%)

therefore, analyzed a large number of cervical cancer patients with stage Ib to IIb cervical cancer who underwent radical hysterectomy including bilateral salpingo-oophorectomy. To our knowledge, the present study is the largest series of patients with ovarian metastasis from cervical cancer.

Material and methods

A total of 3471 patients with International Federation of Gynecology and Obstetrics (FIGO) stage Ib to IIb cervical cancer who underwent radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node dissection (type III) at Hyogo Medical Center for Adults, Aichi Cancer Center Hospital, Jichi Medical School, National Defense Medical College, Saga University Hospital, and Tottori University Hospital between 1981 and 2000 were enrolled in this study. Data were collected from the patients' medical records. Of 3471 patients with cervical cancer, 52 patients (1.50%) had ovarian metastasis. The mean age was 49.9 years old (range 29–73 years). Twenty-six patients were premenopausal women. Tumor size was evaluated with magnetic resonance imaging (MRI) or ultrasonography, and bulky tumor was defined as a maximum diameter over 4 cm. Among 52 patients with ovarian metastasis, 22 patients received radiation alone, 11 patients chemotherapy alone, and 15 patients both radiation and chemotherapy after radical hysterectomy. Four patients did not receive additional treatment after surgery.

Patient survival distribution was calculated using the Kaplan–Meier method. The significance of the survival distribution in each group was tested by a log-rank test. The Chi-square test was used to compare any associations of prognostic factors. Additionally, univariate analysis was done with Stat view Version 4.5-J program (Hulinks Inc, Tokyo Japan) to fit a Cox proportional hazards model. A value of $P < 0.05$ was considered statistically significant.

Results

The incidence of ovarian metastases is shown in Table 1. Patients with ovarian metastases were distributed as follows: 6 in stage Ib1 (3 for squamous cell carcinoma and 3 for adenocarcinoma), 12 in stage Ib2 (one for squamous cell carcinoma and 11 for adenocarcinoma), 5 in stage IIa, and 29 in stage IIb. Twenty-three patients had squamous cell carcinoma, and 29 had adenocarcinoma including adenosquamous cell carcinoma. Ovarian metastasis were more frequently observed in patients with adenocarcinoma than in those with squamous cell carcinoma (5.31% vs. 0.79%, $P < 0.01$).

The 5-year survival rate was 18.0% for patients with adenocarcinoma and 43.5% for those with squamous cell carcinoma, but the difference was not statistically significant (Fig. 1). The 5-year survival rate was 46.6% for stage Ib, 37.5% for stage IIa, and 18.0% for stage IIb. FIGO stage was not significantly related to the prognosis for patients with cervical cancer having ovarian metastasis.

Pathological review could be confirmed in 50 subjects for lymph node involvement and 51 subjects for parametrial invasion. The incident of lymph node involvement and parametrial invasion was 72.0% and 70.5%, respectively. Ovarian metastases did not correlate with lymph node involvement or parametrial invasion (Tables 2, 3). Deep stromal invasion, defined as less than 3 mm from the serosa, could be confirmed in 50 subjects. Endometrial invasion and tumor size could be evaluated in 47 and 44 subjects, respectively. The incidence of deep stromal and endometrial invasion was 80.0% and 55.3%, respectively. Bulky tumor was observed in 54.5% of patients with ovarian metastasis. Parametrial invasion was only the risk factor in patients with ovarian metastasis (Table 4).

Forty patients (76.9%) (16 for squamous cell carcinoma and 24 for adenocarcinoma) had a recurrence: 10 intrapelvic, 23 extrapelvic, 3 both intrapelvic and extrapelvic, and 4 unknown site. Among extrapelvic recurrence, a distant (extraabdominal) recurrence was observed in 18 patients (9 for squamous cell carcinoma and 9 for adenocarcinoma). Three intraabdominal lesions (peritonitis carcimoatosa) occurred among the extrapelvic recurrence. Distant recurrent sites were 7 in bone, 6 in

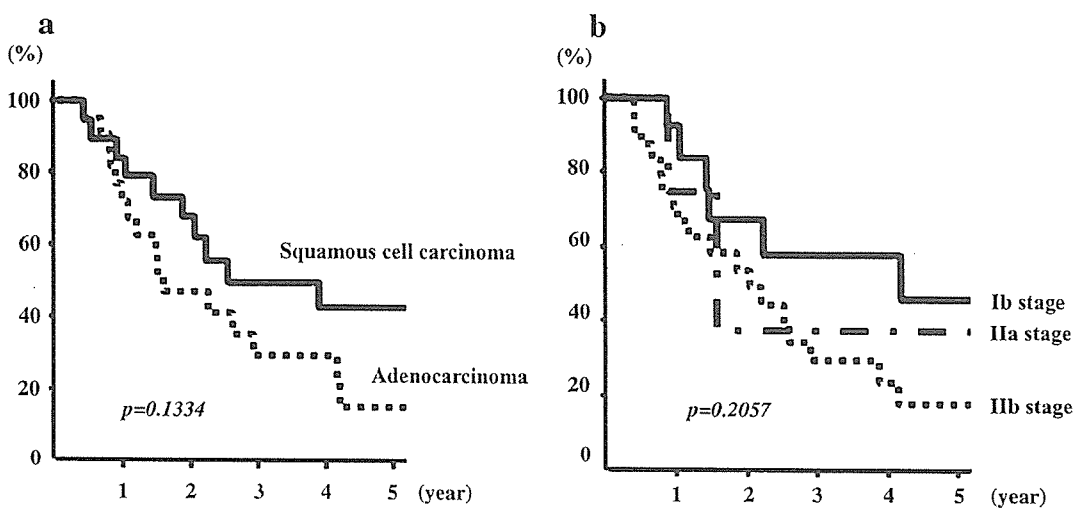

Fig. 1. The survival rate for patients with cervical cancer who have ovarian metastasis. (a) The outcome for patients with adenocarcinoma was worse than that of patients with squamous cell carcinoma, but the difference was not significant. (b) The 5-year survival rate was 46.6% for stage Ib, 37.5% for stage IIa, and 18.0% for stage IIb. FIGO stage did not significantly affect the outcome for patients with cervical cancer having ovarian metastasis.

Table 2
Pelvic lymph node involvement and ovarian metastasis

	Ovarian metastasis		
	Bilateral (n = 21)	Right (n = 11)	Left (n = 18)
Bilateral (n = 30)	16	6	8
Unilateral (n = 6)	1	0	5 (2)
Negative (n = 14)	4	5	5

( ): the same site of ovarian metastasis.

lung, 3 in liver, and 2 in skin. Of 9 distant recurrence patients with squamous cell carcinoma, 8 patients recurred in extra-pelvic lymph node (5 para-aortic lymph node, 2 cervical lymph node, and one inguinal lymph node). Two of 9 distant recurrence patients with adenocarcinoma showed para-aortic lymph node recurrence and remaining 7 had hematogenous metastasis.

Discussion

A review of published studies indicated that the incidence of ovarian metastasis from uterine cervical cancer is less than 0.5% of squamous cell carcinoma and 1.4% of adenocarcinoma [13]. However, the details are not clear due to the small number of subjects studied. Toki et al. reported that one of 525 (0.19%) patients with squamous cell carcinoma and 2 of 36 (5.5%) patients with adenocarcinoma had ovarian metastasis [12]. No patients with stage Ib had ovarian metastasis. Other authors found ovarian metastasis in 9 of 82 (11%) patients with adenocarcinoma (1/40 for stage Ib, 1/5 for stage IIa, and 7/37 for stage IIb) [9]. The largest study until now is Sutton et al.'s [14]. In their study, 990 patients with stage Ib were examined, and ovarian metastasis was identified in 4 of 770 (0.5%) patients with squamous cell carcinoma and 2 of 121 (1.7%) patients with adenocarcinoma [14]. Even their study could not conclude that a significant difference occurred in the incidence of ovarian metastasis between adenocarcinoma and squamous cell carcinoma. In the present study, the incidence of ovarian metastasis from adenocarcinoma of 5.31% (29/546) was significantly higher than that of squamous cell carcinoma (29/2925, 0.79%). Furthermore, we describe the distribution of patients with ovarian metastasis in each stage.

As a result, the incidence of ovarian metastasis in patients with squamous cell carcinoma was less than 1% for stage Ib–IIa, but 2.17% for stage IIb. In contrast, the incidence of ovarian metastases in patients with adenocarcinoma was high in all stages. The incidence of ovarian metastasis in stage Ib patients with adenocarcinoma was the same as in stage IIb patients with squamous cell carcinoma.

Table 3
Parametrial invasion and ovarian metastasis

	Ovarian metastasis		
	Bilateral (n = 20)	Right (n = 13)	Left (n = 18)
Bilateral (n = 16)	6	5	5
Unilateral (n = 20)	8	3 (1)	9 (4)
Negative (n = 15)	6	5	4

( ): the same site of ovarian metastasis.

Table 4
Pelvic lymph node involvement and ovarian metastasis

Risk factor	Numbers	5-year survival rate (%)	P value
Lymph node involvement			
Positive	36	19.6	0.094
Negative	15	46.3	
Paramatrial invasion			
Positive	36	16.4	0.034
Negative	14	58.3	
Deep stromal invasion			
Positive	40	18.2	0.090
Negative	10	44.9	
Endometrial invasion			
Positive	26	35.0	0.525
Negative	21	24.2	
Bulky tumor			
<4 cm	24	33.8	0.921
>4 cm	20	30.7	

Preserving the ovaries is an important issue when deciding about surgery for cervical cancer in young women. In our series, the incidence of ovarian metastasis in stage Ib–IIa patients with squamous cell carcinoma is very low (0.22% for stage Ib and 0.75% for stage IIa). This finding is nearly identical to that of Baltzer et al. (4/745, 0.5%), Singleton et al. (1/258, 0.4%), and Sutton et al. (0.5%) [13–15]. We also recommend preserving the ovaries in stage Ib and IIa patients with squamous cell carcinoma. One author reported that it was reasonable to conserve normal appearing ovaries in young women undergoing radical hysterectomy for treatment of stage Ib cervical adenocarcinoma [9]. On the contrary, another author indicated that ovarian preservation was contraindicated for patients with adenocarcinoma because of its high incidence of ovarian metastasis [12]. We found that the incidence of ovarian metastasis was 3.72% even in stage Ib patients with adenocarcinoma.

In the literature, several risk factors have been proposed, including lymph node involvement, deep stromal invasion, endometrial invasion, and tumor size [7–10,13,16]. The present study showed that the incident of those risk factors ranged from 55% to 80%, and that two patients who had no lymph node involvement, no stromal invasion, no endometrial invasion, and no bulky tumor had ovarian metastasis. Determining whether the patient has ovarian metastasis during surgery is difficult. Our study was unable to detect a predictor of ovarian metastasis; ovarian metastases did not correlate with lymph node involvement or parametrial invasion.

In FIGO report, the 5-year survival rate for patients with cervical cancer was 80.7% for stage Ib, 76.0% for stage IIa, and 73.3% for stage IIb [17]. The current study found that the 5-year survival rate for patients with ovarian metastasis was 46.6% in stage Ib, 37.5% in stage IIa, and 18.0% in stage IIb. Although 48 patients (92.3%) received adjuvant therapy, including radiotherapy and/or chemotherapy after radical hysterectomy, 40 patients had recurrences. Furthermore, 26 of 40 patients (65%) showed distant recurrences,

and the incidence of distant recurrence was more frequent than that of local relapse. The outcome for patients with ovarian metastasis is very poor, indicating that ovarian metastasis is the prognostic factor in patients with cervical cancer. Additionally, the present study revealed that most of the risk factors, such as histology, FIGO stage, and lymph node involvement, were not significant in patients with ovarian metastasis. Parametrial invasion was only the risk factor in patients with ovarian metastasis.

Routes of spread to the ovarian involvement in cervical cancer have been controversial. Wu et al. suggested that lymphatic spread and transtubal implantation might be possible pathways of metastases from cervix to the ovaries [11]. On the other hand, Tabata et al. reported that ovarian metastasis might occur via hematogenous spread of cervical carcinoma [8]. Interestingly, we found that 8 of 9 distant recurrent patients with squamous cell carcinoma showed lymphatic spread. In contrast, 7 of 9 those patients with adenocarcinoma had hematogenous metastasis. Our results suggest that the route of spread to ovarian metastasis from cervical cancer might be different by histological type, while the further study is necessary to draw the conclusion of routes of spread to the ovary.

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Urodynamic study on postsurgical bladder function in cervical cancer treated with systematic nerve-sparing radical hysterectomy

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Abstract. Todo Y, Kuwabara M, Watari H, Ebina Y, Takeda M, Kudo M, Yamamoto R, Sakuragi N. Urodynamic study on postsurgical bladder function in cervical cancer treated with systematic nerve-sparing radical hysterectomy. *Int J Gynecol Cancer* 2006;**16**:369–375.

The objective of this study was to assess the postsurgical bladder function by urodynamic study in patients with cervical cancer treated with nerve-sparing radical hysterectomy. A total of 27 consecutive patients were included in the study. Of the 27 patients, autonomic nerves had been completely preserved at least on one side in 22 patients (group A), and autonomic nerves could not be successfully preserved in five patients (group B). In group A, there was no significant difference in compliance at the moment of strong desire to void, maximum flow rate, and residual urine volume between before the operation and at 12 months after the operation. However, abdominal pressure at maximum flow had significantly increased in patients of group B than of group A. Detrusor contraction pressure at maximum flow had significantly decreased in patients of group B than of group A. Bladder sensation was diminished in three cases (60%) of group B but preserved in all the patients of group A. Although it is still preliminary, our surgical technique described in this report is thought to be effective for preservation of bladder function. For further evaluation of the efficacy of nerve-sparing radical hysterectomy in terms of quality of life and survival of patients, a prospective randomized trial needs to be performed.

KEYWORDS: autonomic nerve, bladder function, cervical cancer, nerve-sparing, radical hysterectomy, urodynamic study.

The quality of life (QoL) of patients who have undergone radical hysterectomy is deteriorated by physical and mental stress caused by difficulty in urination after the operation. The reported incidence of impaired bladder function at 12 months after radical hysterectomy is as high as 63% for sensory loss, 55% for stress incontinence, and 85% for urination with abdominal pressure (Pabd) as well as 63% for abnormal compliance[1]. Various attempts for preserving urinary function, including recently proposed autonomic nerve-preserving radical hysterectomy techniques, have been reported[2–6].

Several studies have been carried out on urodynamics after radical hysterectomy, but the results are discrepant. The reason for this discrepancy is thought to be differences in operations and periods of examination. There have been very few reports in which the type of operation and the time of examination has been clearly stated and in which preoperative and short-term as well as long-term postoperative data are compared. In this study, we assessed urodynamic results of radical hysterectomy with autonomic nerve preservation in patients with uterine cancer.

Materials and methods

A total of 27 patients who underwent radical hysterectomy during the period from January 2000 to December 2002 and in whom urodynamic examinations were performed before radical hysterectomy and at 1 month and 3, 6, and 12 months after the operation were included in this study. Of these 27 patients, data for 22 patients (group A) in whom autonomic nerves had been completely preserved at least on one side and

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data for five patients (group B) in whom the autonomic nerves had not been successfully preserved were used for analysis. The clinical backgrounds of the 27 patients are shown in Table 1. The ages of the 22 patients of group A ranged from 35 to 60 years (median age: 43 years) and those of the five patients of group B ranged from 31 to 64 years (median age: 46 years). In group A, there were six patients with stage IB1, six with stage IB2, three with stage IIA, and seven with stage IIB uterine cervical cancer. For stage IIB patients, nerve-sparing procedure was employed for only the uninvaded side. In group B, there were four patients with stage IB1 and one patient with stage IIB uterine cervical cancer. None of the patients underwent radiation therapy before the operation, but radiation therapy was performed in three patients of group A postoperatively. None of the patients took cholinergic agents or α1 blocker during the observation period.

Operative procedure

Nerve-sparing radical hysterectomy was performed as described in the preceding report. Briefly, the following surgical procedure was used, which is based on the anatomical consideration for autonomic nerves innervating urinary bladder[6]. Before hysterectomy, the pelvic lymph nodes were removed. The hypogastric nerves and the proximal part of the pelvic plexus were identified and lateralized during the dissection of the uterosacral ligament and rectovaginal ligament. After lateralizing the hypogastric nerves and the proximal part of the pelvic plexus, the nerve tissue in this part could be preserved by selective resection of the exposed uterosacral and rectovaginal ligaments. We carefully attempted to avoid dissecting pelvic splanchnic nerves together with the vascular part of the cardinal ligament during resection of the cardinal ligament. In this part of the technique, first, the cardinal ligament nodes were dissected to clearly skeletonize the deep uterine vein using suction apparatus. The uterus was then pulled up in the direction perpendicular to the operating table to expose two separate parts: the cardinal ligament that contains vessels, fat, and loose connective tissue and the dorsomedial part below the cardinal ligament that contains nerve fibers. The anterior segment of the vesicouterine ligament was dissected after developing the ureteral tunnel. Since vesical vein was draining from bladder to deep uterine vein coursing through the posterior part of the vesicouterine ligament, separation and cutting of the vesical vein was required for resection of the uterus. The fatty connective tissue of the posterior part of the vesicouterine ligament was resected while leaving the vesical nerve branches of the pelvic plexus. This enabled identification of the plain between the pelvic plexus and the paracolpium. The blood vessels of the cardinal ligament were resected at the origin of the vessels from internal iliac vein. The careful rubbing of the deep uterine vein in an upward (ventral) direction to its point of attachment to the paracolpium enabled sparing of the

Table 1. Clinical profile of 27 patients with cervical cancer who underwent radical hysterectomy

	Group A ($n = 22$)	Group B ($n = 5$)	P value
Age (in years)	35–60 (median: 43)	31–64 (median: 46)	0.41
Stage			
IB1	6	4	
IB2	6	0	
IIA	3	0	
IIB	7	1	0.15
Tumor diameter (mm)	11–70 (median: 39)	12–50 (median: 34)	0.57
Length of resected vagina (mm)	20–45 (median: 30)	25–35 (median: 35)	0.30
Adjuvant Tx			
None	4	2	
RT	1	0	
CHT	15	3	
RT + CHT	2	0	0.82
Symptoms at 12 months			
Incontinence	0	3	0.0034
Abnormal sensation	2 (increased sensation)	3 (decreased sensation)	0.030
Recurrence	1[a]	0	>0.99
Duration of DFS (months)	13–48 (median: 30)	12–36 (median: 32)	0.90

Tx, treatment; RT, radiation therapy; CHT, chemotherapy; DFS, disease-free survival.
[a]Patient was in stage IIB, and recurrence occurred in the pelvis 13 months after surgery, which was treated with radiation therapy, and she is alive with no evidence of disease at the moment of preparing this article.

lower (dorsomedial) nerve tissue. The space between the pelvic plexus and the paracolpium was developed anteroposteriorly by using Kelly forceps or Metzenbaum scissors. From this approach, the pelvic plexus was put away laterally. Then the uterine branch of the pelvic plexus was cut, which enabled dissection of the paracolpium without involving the pelvic plexus.

For the five patients of group B, the nerve-sparing procedure could not be successfully performed due to bleeding from the paracolpium and/or the surgeon's inexperience, although we had an intension to preserve the nerves. The space between the pelvic plexus and the paracolpium could not be developed, and therefore, the pelvic plexus could not be put aside. The vaginal canal was cut without selective dissection of the uterine branches of the pelvic plexus for the cases of group B.

Postoperative treatment

Postoperative whole-pelvic external radiation therapy (50 Gy) was employed when there was lymph node metastasis or histologically confirmed parametrial invasion. When the tumor had invaded the lymphatic or vascular channels, we treated the patient with cisplatin-based chemotherapy for 3–6 cycles, unless the patient refused this treatment. The follow-up period ranged from 12 to 48 months (median: 29 months).

Urodynamic study

Urodynamic studies were carried out before the operation and at 1 month and, 3, 6, and 12 months after the operation. The urodynamic studies were carried out using a Urolab spectrum™ (Life-Tech Inc., Stafford, TX) by the following procedure. A 7F double-lumen catheter for cystometrography (DLC-7D; Life-Tech Inc.) was placed in the urethra after collecting residual urine, and a balloon catheter for measuring rectal internal pressure (RPC-9D; Life-Tech Inc.) was inserted into the rectum. While the patient was sitting on a toilet seat, saline solution was continuously infused through the catheter into the urethra at a rate of 30 mL/min. Maximum cystometric capacity was defined as the capacity at the time of the strongest desire to void, the time when 700 mL of saline solution had been infused in the patients having no desire to void, or the time of persistent urinary incontinence if urinary incontinence occurred before the desire to void. Vesical volume, vesical pressure, Pabd, and urinary flow volume were monitored simultaneously. Detrusor contraction pressure was automatically calculated by subtracting Pabd from vesical pressure. Urodynamic evaluators were bladder compliance (Cves) at the moment of strong desire to void, maximum flow rate (MFR), detrusor contraction pressure at maximum flow (Pdet Qmax), abdominal pressure at maximum flow (Pabd Qmax), and residual urine volume. The problem in analysis of the voiding phase is that there is a lack of data for patients in whom voiding is impossible due to psychologic stress. Since no data for Pabd Qmax and Pdet Qmax could be obtained from some of the present patients in the early postoperative period due to voiding incompetence, these pressures were analyzed preoperatively and at 6 and 12 months postoperatively. Maximum urinary flow rate was taken as 0.0 mL/sec for patients who were not able to void in tests carried out at 1 month and at 3 months after the operation. Bladder sensation was categorized into four levels: (1) normal: a patient felt a desire to void when 200 mL or more of saline solution was infused; (2) increased: a patient felt a strong desire to void when less than 200 mL of saline solution was infused; (3) reduced: a patient merely felt an obscure tension of the bladder when 400 mL or more of saline solution was infused; and (4) absent: a patient did not feel a tension of the bladder when 400 mL or more of saline solution was infused or persistent urinary incontinence occurred before the desire to void. All the terms and symbols used for parameters in this paper were taken from the 1988 report by the International Continence Society.

Statistical analysis

Categorical variables were analyzed using the χ^2 test or Fisher exact test. Median values of continuous variables were compared by the Mann–Whitney U test. Whether our procedure had an impact on each parameter or not was analyzed by repeated measure one-way analysis of variance (ANOVA), and significance in differences between time points was examined using Fisher's protected least significant difference test when significant differences were indicated by the results of repeated measure one-way ANOVA. The comparison between group A and group B was analyzed by repeated measure two-way ANOVA. A result was deemed significant when $P < 0.05$.

Results

Comparison of the results of urodynamic study between patients with and without successful autonomic nerve preservation

Results of urodynamic studies performed 110 times in group A are shown in Table 2. Data were obtained

Table 2. Urodynamic values of 22 patients in whom autonomic nerves had been preserved

	Number of cases	Before surgery (mean ± SD)	After surgery (months)			
			1	3	6	12
Storage phase						
Cves at SDV (mL/cmH_2O)	22	64.0 ± 63.4	12.9 ± 14.2*	31.4 ± 39.1*	41.3 ± 45.9*	67.8 ± 71.8
Voiding phase						
MFR (mL/sec)	21	19.6 ± 8.5	8.9 ± 7.3*	10.2 ± 7.2*	13.8 ± 8.7*	16.5 ± 10.1
Pabd Qmax (cmH_2O)	20	5.5 ± 24.2			19.4 ± 24.4*	13.9 ± 22.5*
Pde Qmax (cmH_2O)	20	38.1 ± 17.1			26.5 ± 17.4*	26.8 ± 14.7*
Residual urine	22	6.8 ± 10.6	126.9 ± 125.2*	90.5 ± 115.2*	34.6 ± 58.9*	16.5 ± 34.4

SDV, strong desire to void.
*$P < 0.05$ compared to preoperative value.

from all the patients in the storage phase, but data for three patients (one patient who could not void in the preoperative test, one patient for whom a problem occurred in testing before the operation, and one patient for whom a problem occurred in testing at 12 months after the operation) were not included in the analysis in the voiding phase. Data for two patients, one who could not void in the test carried out before the operation and one who could not void in the test carried out at 12 months after the operation, were not included in the analysis at the time of MFR. Results of urodynamic studies performed 25 times in group B are shown in Table 3.

There was no significant difference in Cves of group A between before the operation and at 12 months after the operation, but Cves of group B at 12 months after the operation was significantly lower than that before the operation. Repeated measure two-way ANOVA revealed that the adverse effect on Cves in group B was significantly more than that in group A ($P < 0.05$, Fig. 1).

There was no significant difference in MFR of group A between before the operation and at 12 months after the operation, but MFR of group B at 12 months after the operation was significantly lower than that before the operation. There was no significant difference in MFR between groups A and B (Fig. 2).

The Pabd Qmax of either group A or group B at 12 months after the operation was significantly higher than that before the operation. The adverse effect on Pabd in group B was significantly more than that in group A ($P < 0.05$, Fig. 3).

The Pdet Qmax of either group A or group B at 12 months after the operation was significantly lower than that before the operation. The adverse effect on Pdet Qmax in group B was significantly more than that in group A ($P < 0.01$, Fig. 4).

The residual urine volume of group A was almost the same as the preoperative volume at 12 months after the operation. The adverse effect on residual urine volume in group B was significantly more than that in group A ($P < 0.05$, Fig. 5).

The effect of postoperative treatment on the results of postoperative urodynamic study

The radiation therapy was given to 3 of the 22 patients in group A postoperatively. Among the urodynamic variables, Cves seemed to be adversely affected by radiation therapy. Cves in 19 nonirradiated patients decreased to the nadir value at 1 month after operation and increased steadily thereafter during the follow-up period after operation and returned to preoperative value at 12 months after the operation. On

Table 3. Urodynamic values of five patients in whom autonomic nerves had not been preserved

	Number of cases	Before surgery (mean ± SD)	After surgery (months)			
			1	3	6	12
Storage phase						
Cves at SDV (mL/cmH_2O)	5	163.8 ± 167.9	9.8 ± 7.6*	32.2 ± 19.7*	32.3 ± 28.4*	59.3 ± 36.9*
Voiding phase						
MFR (mL/sec)	5	17.0 ± 3.3	3.1 ± 3.6*	6.2 ± 7.2*	7.7 ± 6.8*	10.8 ± 5.0*
Pabd Qmax (cmH_2O)	5	1.0 ± 18.1			21.8 ± 24.2	40.2 ± 27.5*
Pde Qmax (cmH_2O)	5	44.0 ± 15.7			28.6 ± 20.0	8.6 ± 12.2*
Residual urine	5	3.6 ± 4.0	251.2 ± 227.0*	274.2 ± 245.6*	145.2 ± 136.5	88.2 ± 87.8

SDV, strong desire to void.
*$P < 0.05$ compared to preoperative value.

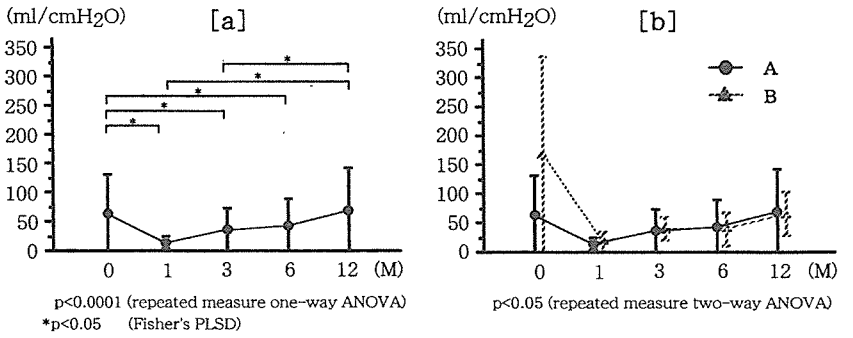

Figure 1. Cves at strong desire to void. a) Preoperative and postoperative measurement in group A patients. b) Comparison of changes in measurement between groups A and B.

contrary, Cves in three irradiated patients further decreased after 1 month of operation and reached nadir value at 6 months after the operation. The Cves remained at decreased level even 12 months after the operation. The postoperative radiation was suggested to impair the recovery of Cves, although the difference between the two patients groups did not reach a statistically significant level ($P = 0.087$).

Discussion

The incidence of urinary tract injuries in radical hysterectomy has been decreasing in recent years due to improvements in surgical techniques. Much interest has recently been shown in autonomic nerve-sparing surgical techniques[2–6].

There have been many studies on urodynamics after radical hysterectomy, but a consensus regarding urodynamics has not been reached. One reason for this is that surgical techniques used for radical hysterectomy have not been clearly described in many reports. Piver *et al.* proposed five classes for the extent of radical hysterectomy[7], and this classification is often used now for discriminating types of operation. The surgical technique of Wertheim–Meigs is considered to correspond to type III[8]. In radical hysterectomy, pelvic plexus is in close proximity to the paracolpium at the depth at which the vagina should be dissected. If separation of the pelvic plexus from the paracolpium is insufficient, the pelvic plexus will be injured at the time of amputation of vagina. Possover *et al.* recently reported that preservation of the pelvic splanchnic nerves and pelvic plexus, with the middle rectal artery serving as a landmark for identification, is important for preserving bladder function[6]. If the cardinal ligament below the middle rectal artery is dissected, the pelvic splanchnic nerves will be injured. Moreover, if the uterosacral ligaments are excised at their sacral attachments, the hypogastric nerves and the pelvic plexus may be also excised. Therefore, it is not clear in a simple statement that a type III operation was performed, whether hypogastric nerves, the pelvic splanchnic nerves, and the pelvic plexus were preserved or not. Thus, accurate evaluation of bladder dysfunction after radical hysterectomy is not possible without detailed information on the surgical procedure used.

Another important point in discussing urodynamics after radical hysterectomy is comparison of preoperative and postoperative test results. It has been reported

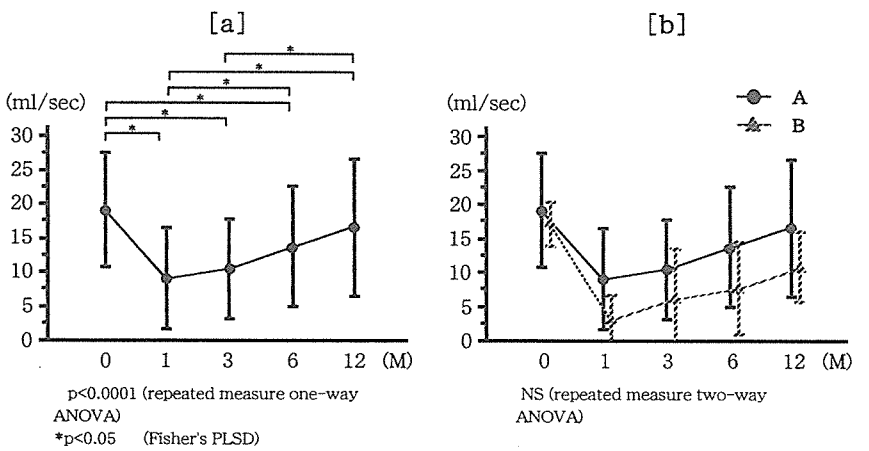

Figure 2. MFR. a) Preoperative and postoperative measurement in group A patients. b) Comparison of changes in measurement between groups A and B.

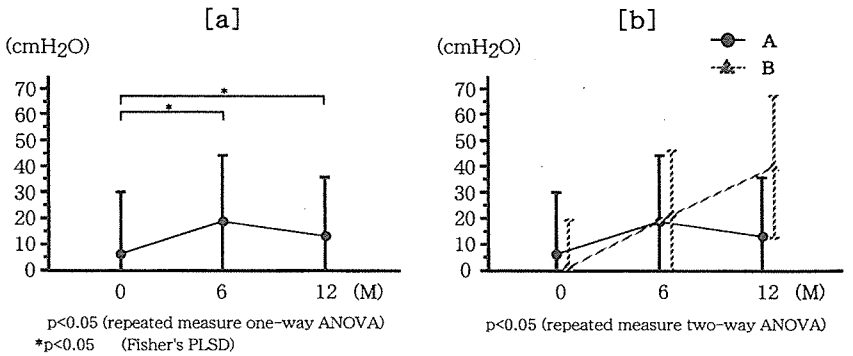

Figure 3. Pabd Qmax. a) Preoperative and postoperative measurement in group A patients. b) Comparison of changes in measurement between groups A and B.

that about 80% of patients with uterine cervical cancer already have some degree of bladder dysfunction before undergoing surgery[9]. It would not be possible to determine whether poor Cves is due to the operation or due to a dysfunction that already existed before the operation, if preoperative tests were not carried out. There has been criticism of studies in which urodynamic analysis was only carried out after the operation[10]. Other important points for urodynamic studies of urinary function after radical hysterectomy are to conduct tests on the subjects at the same time for comparison of results among the subjects and to carry out not only short-term but also long-term assessments. Voiding dysfunction symptoms after radical hysterectomy have been thought to disappear within 6–12 months after the operation[11,12]. However, urodynamic studies have revealed that there does exist underlying bladder dysfunction after 12 months of operation[13].

In this study, the results showed that our technique does not cause a deterioration in Cves and MFR and an increase in residual urine volume at 12 months after the operation, although it does cause some amount of increase in Pabd Qmax and reduction in Pdet Qmax. Actually, there was no patient who complained of urinary difficulty at 12 months after the operation, which was confirmed by a urodynamic study and a questionnaire. That is to say, radical hysterectomy combined with autonomic nerve preservation did not cause significant deterioration in QoL of our patients. There have been very few reports in which the surgical technique used and the timing of tests are clearly described, preoperative and postoperative values for all the patients are compared, and results of both short-term and long-term tests are presented. Such description and presentation of results appear in a report by Scotti *et al.*, but, unfortunately, type II operations were performed on half of their patients[14]. In our experience, bladder dysfunction is rarely a problem in a type II operation.

We employ our technique for autonomic nerve preservation to the uninvaded side for patients with stage IIB uterine cervical cancer. It is reported that the normal urinary function could be maintained when at least one side of the sympathetic nerve was preserved in experimental animals[15]. This data suggest that the normal urinary function can be maintained by applying the operation with autonomic nerve preservation to the noninvaded side in patients with stage IIB cervical cancer who had parametrial invasion only at one side.

Piver's type III (Wertheim–Meigs) operation is the treatment of choice for FIGO stages IB–IIA cervical cancer in Western countries. The standard treatment

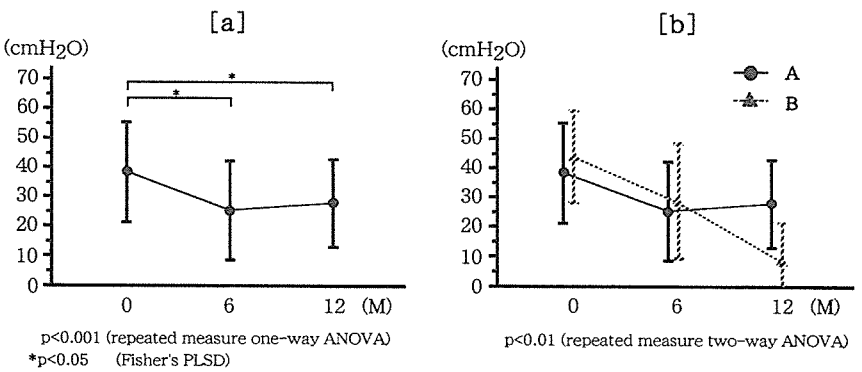

Figure 4. Pde Qmax. a) Preoperative and postoperative measurement in group A patients. b) Comparison of changes in measurement between groups A and B.

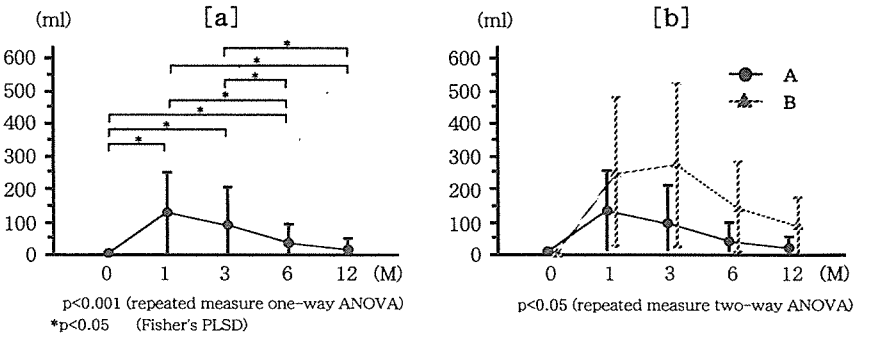

Figure 5. Residual urine volume. a) Preoperative and postoperative measurement in group A patients. b) Comparison of changes in measurement between groups A and B.

for patients with stages IB–IIB cervical cancer in Japan is radical hysterectomy originally described by Okabayashi[16]. This surgery is more radical than Wertheim hysterectomy. According to the recent statistics regarding treatment of cervical cancer announced from the Japan Society of Obstetrics and Gynecology[17], only 4% of patients with stage IIB cervical cancer received primary radiotherapy. Concurrent chemoradiation is not a standard treatment in Japan at this moment. The radiation therapy will cause permanent loss of ovarian function and sexual disturbance due to fibrous stenosis of vaginal canal, and these are quite detrimental for sexually active women. We have performed procedures for preserving ovarian function and preventing shortening of the vagina[8–21] in an attempt to maintain QoL of patients with cervical cancer treated with radical hysterectomy. Regarding chemoradiation, however, a large-scale clinical trial needs to be conducted in Japan too.

In conclusion, our aim seems to have been achieved because the urinary function, both subjectively and objectively, at 12 months after operation is almost normal.

Acknowledgment

The authors wish to thank Dr Kenichi Oguchi for his contribution to introducing urodynamic analysis in the care of patients undergoing radical hysterectomy, without whom our attempts would not have been started and completed.

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EDITORIAL

Is paclitaxel/carboplatin really a useful regimen for ovarian cancer compared with platinum/doxorubicin/cyclophosphamide?

Article on page 221

Historical control study of paclitaxel–carboplatin (TJ) versus conventional platinum-based chemotherapy (CAP) for epithelial ovarian cancer

R. Numazaki, E. Miyagi, R. Onose, T. Nakazawa, K. Sugiura, K. Asukai, H. Nakayama, A. Miyamatsu, N. Okamoto, F. Hirahara

In this issue of the *International Journal of Clinical Oncology*, Numazaki et al.[1] report the efficacy and toxicity of paclitaxel/carboplatin compared with platinum/doxorubicin/cyclophosphamide. In general, the purpose of this study and the direction of the discussion are well considered and documented, and we can know, in general, the efficacy and toxicity of practical treatments with paclitaxel/carboplatin in Japanese women with ovarian cancer. Unfortunately, three major problems in this study need to be clarified.

1. This is not a protocol study, but, rather, a comparison of practical treatments. On this point, the article seems confused.
2. As for the anti-tumor effects of paclitaxel/carboplatin reported, they neither fit the response evaluation criteria in solid tumors (RECIST) or the criteria set by the Japan Society of Clinical Oncology (JSCO), but are evaluated by the authors' specific criteria. Although all the patients with disease stages III/IV were evaluated for effects, in terms of lesions on images, it cannot be considered as common sense that all patients with III /IV disease after standard surgery will have measurable lesions, as was described in this article.
3. Because there were differences in the use of granulocyte-colorn-stimulating factor (G-CSF) and a 5-HT3 antagonist over time, a toxicity comparison of the groups cannot be done. In fact, there were no treatment discontinuations in the group with paclitaxel-carboplatin (TJ) which showed severe blood toxicity (grade 3/4), whereas there were patients who discontinued the platinum-based chemotherapy (CAP).

I feel that this article could be more useful if a study of the effects of TJ treatment and toxicity, and the results in subjects with stage III/IV cancers were to be addressed and compared with the results of past (CAP) therapy, which has been described in the Discussion section.

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Treatment results of adjuvant chemotherapy after radical hysterectomy for intermediate- and high-risk stage IB–IIA cervical cancer

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Abstract

Objective. To determine the effectiveness of chemotherapy alone as postoperative adjuvant therapy for intermediate- and high-risk cervical cancer.

Methods. The study group comprised of 65 consecutive patients with stage IB or IIA squamous cell or adenosquamous cervical cancer who were initially treated with radical hysterectomy and pelvic lymphadenectomy between 1993 and 2002. Tumors were of intermediate-risk (stromal invasion > 50%, $n = 30$) or high-risk (positive surgical margin, parametrial invasion, and/or lymph node involvement, $n = 35$). In all cases, chemotherapy was administered adjuvantly: three courses of bleomycin, vincristine, mitomycin, and cisplatin for intermediate-risk cases and five courses for high-risk cases. Disease-free survival and complications of the combined therapy were investigated.

Results. Estimated 5-year disease-free survival was 93.3% for the 30 patients with intermediate-risk tumors (100% for those with squamous cell carcinoma and 71.4% for those with adenosquamous carcinoma) and 85.7% for the 35 patients with high-risk tumors (89.3% for those with squamous cell carcinoma and 71.4% for those with adenosquamous carcinoma). The incidence of locoregional recurrence was 3.3% in the intermediate-risk group and 8.6% in the high-risk group. Side effects of chemotherapy and complications of the combined therapy were within acceptable limits. No patient had severe bleomycin-related pulmonary toxicity. Only 1.5% of patients developed small bowel obstruction, which was cured by conservative therapy.

Conclusions. The treatment results suggest the potential role of adjuvant chemotherapy alone for patients with cervical cancer.

Keywords: Cervical cancer; Chemotherapy; Adjuvant therapy

Introduction

Radiotherapy (RT) has been used as postoperative adjuvant therapy to reduce recurrence in patients with cervical cancer. For patients with intermediate-risk tumors, i.e., cervical cancer showing deep stromal invasion and/or capillary space involvement but no lymph node metastasis, the effectiveness of RT has been widely accepted, based on the cure rate [1] and the results of a randomized study reported by Sedlis et al. [2]. For patients with node-positive cervical cancer, however, reports on the outcome of postoperative RT have implied that adjuvant RT alone may change the pattern of recurrence from intrapelvic to extrapelvic but offer little survival benefit [3–6]. In 2000, Peters et al. [7] advocated a new strategy for treating high-risk cervical cancer. They showed a significant survival advantage with the use of concurrent chemoradiation (CCR) rather than RT alone in patients with high-risk cervical cancer.

The debate regarding the role of adjuvant therapy for cervical cancer patients has generally focused on RT or CCR, but several studies have suggested the utility of chemotherapy (CT) alone as postoperative adjuvant therapy for cervical cancer. Lahousen et al. [8] prospectively compared adjuvant CT with RT in patients with high-risk cervical cancer and concluded that neither of the regimens improved survival or the rate of recurrence. In that study, however, the 5-year survival rate was about 80% among 19 patients with nodal disease who received CT. Iwasaka et al. [9] reported an 83% 5-year survival rate among

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patients with high-risk cervical cancer treated adjuvantly with CT. They also reported an advantage of CT in the treatment of local failure. These findings suggest that the value of CT as adjuvant therapy for cervical cancer is worth reexamining.

At our institute, CT alone has been used as postoperative adjuvant therapy for cervical cancer since 1993. Herein, we report the treatment results among patients with stage IB–IIA squamous cell or adenosquamous cervical cancer, all of whom were treated initially by radical hysterectomy, had intermediate- or high-risk tumors, and received CT postoperatively.

Patients and methods

Between 1993 and 2002, 233 patients with stage IB–IIA squamous cell or adenosquamous cervical cancer underwent radical hysterectomy and pelvic lymphadenectomy at the Cancer Institute Hospital (Tokyo, Japan). None of the patients had received any treatment prior to surgery. After pathologic assessment, patients who were identified as having intermediate- or high-risk tumors were scheduled to receive postoperative adjuvant CT without RT.

The criteria for intermediate-risk tumors were the presence of more than 50% cervical stromal invasion and the absence of high-risk factors. The presence or absence of lymph-vascular space involvement and tumor size does not alter these criteria. The criterion for high-risk tumors was the presence of at least one of the three following factors: histologically confirmed positive lymph nodes, parametrial invasion, and a positive surgical margin.

Of the 233 patients, 35 were identified as having intermediate-risk tumors, but five of these patients were excluded from the study. None of the five patients received CT; three refused it and two had medical problems. One of the five patients received RT. Forty patients were identified as having high-risk tumors, but five were excluded from the study. One patient refused CT and ultimately received no adjuvant therapy. The remaining four patients received CT, but one patient also received RT, two received a different regimen of CT, and the last patient died of primary lung cancer 6 months after treatment. Thus, 30 patients with intermediate-risk tumors and 35 patients with high-risk tumors were the study subjects. Patient characteristics are listed in Table 1.

Table 1
Patient characteristics

	Intermediate-risk n = 30	High-risk n = 35
Median age in years (range)	49 (28–70)	43 (25–68)
Clinical stage		
Stage IB1	16	20
Stage IB2	12	12
Stage IIA	2	3
Cell type		
Squamous	23	28
Adenosquamous	7	7
Stromal invasion		
Inner half	0	10
Outer half	30	25
Lymph-vascular space involvement		
No	13	7
Yes	17	28
Positive pelvic nodes		
No	30	4
Yes	0	31
Parametrial involvement		
No	30	27
Yes	0	8
Positive margins		
No	30	30
Yes	0	5

Table 2
Relapse rates and sites of failure

Recurrence	Intermediate-risk (n = 30)	High-risk (n = 35)
Locoregional recurrence	1 (3.3%)	3 (8.6%)
Distant recurrence	1 (3.3%)	2 (5.7%)
Both	0	0
Total	2 (6.7%)	5 (14.3%)

Throughout the study period, only CT was administered as postoperative adjuvant therapy, with a single regimen (modified BOMP) being used. The chemotherapy regimen has been described elsewhere [10]. In brief, it consisted of bleomycin (5 mg in 500 mL saline infused intravenously [IV] continuously for 7 consecutive days), vincristine (0.7 mg/m^2 as an IV bolus on day 7), mitomycin (7 mg/m^2 as an IV bolus on day 7), and cisplatin (10 mg/m^2 dissolved in 500 mL saline and infused over 4 h on days 1 through 7). This regimen was scheduled to be repeated every 4 weeks for three cycles in patients with intermediate-risk tumors and five cycles in those with high-risk tumors. The number of CT cycles was based on our prior experience with this CT regimen. For objective targets, the median number of cycles per patient was four [10].

The disease-free interval, sites of relapse, and the morbidity after treatment were investigated in the study patients. Median follow-up time for surviving patients was 75 (range, 39–132) months in the intermediate-risk group and 74 (range, 38–126) months in the high-risk group. Disease-free survival was calculated by the Kaplan–Meier method and was compared by the log-rank test.

Results

Treatment outcome

Two (6.7%) of the 30 patients with intermediate-risk disease suffered recurrence (Table 2). One of these two patients suffered recurrence in the pelvic cavity 18 months after treatment, and the other suffered multifocal recurrence in the liver and lung 11 months after treatment. These two cases were of the adenosquamous cell type. None of the 23 patients with intermediate-risk squamous cell carcinoma suffered recurrence. The estimated 5-year disease-free survival rate in this group was 93.3% (100% for patients with squamous cell carcinoma and 71.4% for those with adenosquamous carcinoma) (Fig. 1).

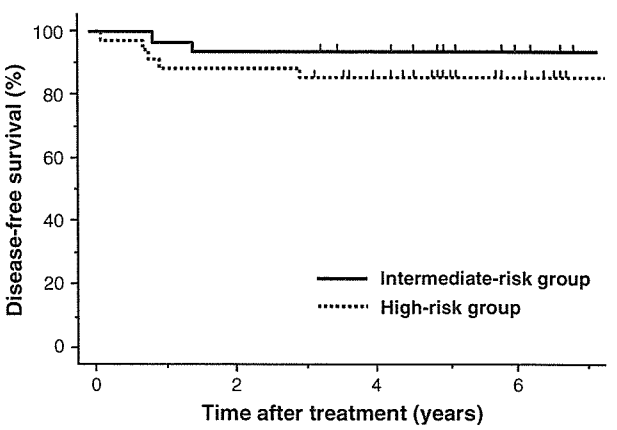

Fig. 1. Disease-free survival of patients with intermediate- and high-risk cervical cancer. Estimated 5-year disease-free survival rates were 93.3% for the 30 patients with intermediate-risk disease and 85.7% for the 35 patients with high-risk disease. No significant difference was noted between the two groups (P = 0.3122, log-rank test).

Five (14.3%) of the 35 patients with high-risk disease suffered recurrence. Three suffered locoregional recurrence, and the remaining two patients suffered distant recurrence (Table 2). Of the 28 patients with high-risk squamous cell carcinoma, three (10.7%) suffered recurrence, whereas two of the seven patients with high-risk adenosquamous carcinoma (28.6%) suffered recurrence. The estimated 5-year disease-free survival rate in the high-risk group was 85.7% (89.3% for patients with squamous cell carcinoma and 71.4% for those with adenosquamous carcinoma). Survival did not differ significantly between the intermediate- and high-risk groups ($P = 0.3122$) (Fig. 1).

Four patients with locoregional recurrence were treated chiefly with RT, but none survived. The three patients with distant recurrence were treated by CT other than the BOMP regimen, but all died from the disease.

Chemotherapy tolerance and toxicity

Of the intermediate-risk patients, seven (23.3%) were unable to complete three cycles of CT; one completed one cycle and six completed two cycles. Of the high-risk patients, 10 (28.6%) were unable to complete five cycles of CT; two completed two cycles, three completed three cycles, and five completed four cycles. In most cases, the patients refused to continue chemotherapy due to CT-related nausea and vomiting.

Side effects of adjuvant CT were within acceptable limits. No patient had severe bleomycin-related pulmonary toxicity or cisplatin-related renal dysfunction. Bleomycin-related dermatitis was observed in one patient. Grade 3 or 4 myelosuppression was observed in 16.7% (5/30) of the intermediate-risk group and 31.4% (11/35) of the high-risk group, respectively.

Complications of the combined therapy

Complications requiring surgical intervention occurred in 2 (3.1%) of the 65 patients, none of which was related to tumor recurrence (Table 3). In one of the two patients, herniation of the abdominal wall was surgically repaired 7 months after the initial surgery. In the other patient, hydronephrosis requiring catheterization between the bladder and kidney was found 10 days after surgery. No patient developed urinary fistula. One patient (1.5%) suffered small bowel obstruction, but this was cured by conservative therapy. Three patients (4.6%) suffered locoregional infection (pelvic lymphcyst, $n = 2$; leg cellulitis, $n = 1$), all of whom were cured without surgical intervention.

Table 3
Complications of combined therapy ($n = 65$)

Complication	No. of cases (requiring surgery)
Gastrointestinal	
Small bowel obstruction	1 (0)
Genitourinary	
Hydronephrosis	3 (1)
Infectious	
Pelvic lymphcyst	2 (0)
Leg cellulitis	1 (0)
Other	
Herniation of the abdominal wall	1 (1)

Discussion

RT has long been used as postoperative adjuvant therapy for stages IB and IIA cervical cancer. In a prospective study of postsurgical patients treated for intermediate-risk cervical cancer, Sedlis et al. [2] showed that adjuvant pelvic RT reduced recurrence from 28% to 15% at 2 years after treatment. Because node-positive cases were excluded from that study, the effectiveness of RT alone for high-risk cervical cancer was unclear, but results suggest that RT has a role in adjuvant therapy. For postsurgical patients with high-risk disease, however, it has been reported that RT alone may decrease the local failure rate, but provide no survival benefit (3–6). Although the necessity of systemic therapy for patients with high-risk disease has been suggested, several studies prospectively examined the effectiveness of CT followed by RT in patients with high-risk cervical cancer in an attempt to reduce both local and distant recurrence, but most of these studies failed to show any survival advantage [11,12]. This problem was resolved by Peters et al. [7]. They examined two treatment modalities, RT and CCR, in 243 patients with high-risk cervical cancer (207 node-positive patients) and obtained 4-year disease-free survival rates of 63% and 80%, respectively. Thus, RT for intermediate-risk postsurgical patients and CCR for high-risk postsurgical patients are at this time considered the optimum treatments. CCR may also be applicable for intermediate-risk tumors.

Despite this worldwide trend, we have consistently treated patients who have undergone surgery for cervical cancer with CT alone for several reasons. First, distant metastasis is a major problem when RT alone is used to treat high-risk cervical cancer, and CT is considered the most powerful means of eradicating subclinical distant metastases. If RT is added to CT, the CT dosage is limited. Second, our CT regimen yielded a 76% response rate in patients with recurrent cervical cancer and an acceptable incidence of side effects [10]; this response rate is much better than that of other recent studies [13]. Third, when CT alone is used for adjuvant therapy, RT can be reserved for local recurrence, simplifying treatment of local recurrence should it occur. Finally, this treatment strategy may provide a better postoperative quality of life by precluding radiation-related morbidity, such as small bowel obstruction or leg lymphedema. Conversely, the biggest concern is that the possibility for local recurrence may increase in the absence of pelvic RT.

Data from the current study indicate that suppression of distant metastasis by means of postoperative CT is feasible in both intermediate- and high-risk patients. One of thirty patients with intermediate-risk disease and 2 of 35 patients with high-risk suffered distant metastasis. More importantly, few patients suffered local recurrence. Despite the absence of pelvic RT, only 3.3% (1/30) of intermediate-risk patients and 8.6% (3/35) of high-risk patients developed locoregional recurrence. Iwasaka et al. [9] performed adjuvant CT (three courses of cisplatin, vincristine, mitomycin, and pepleomycin) for high-risk cervical cancer and compared their patients with those from another hospital where adjuvant RT was performed during the same period. The results of CT (an 83% 5-year

survival rate) were similar to those of RT (an 81.7% 5-year survival rate). In that study, however, intra- and extrapelvic recurrences accounted for 85% and 23%, respectively, of all recurrences in the CT group. A relatively high incidence of local recurrence in patients with high-risk cervical cancer (14.3%, 4/28) treated with CT alone (six courses of carboplatin and bleomycin) was also reported by Lahousen et al. [8]. Both studies included stage IIB cancers, and we assume that the majority of cases of local recurrence were cases of stage IIB disease. Data from the current study, which included stage IB and IIA cancers, suggest that intrapelvic recurrence is not a major obstacle when CT alone is used as adjuvant therapy.

With respect to treatment of local recurrence, Iwasaka et al. [9] reported that 45% of patients with local recurrence in the CT group survived. Because there were only four cases with local recurrence in the current series, we were unable to confirm this finding. In our study, all patients with local recurrence were treated by full dose of RT, but none survived. However, in the Lahousen et al. study [8], four of the eight patients with pelvic recurrence in their CT group survived. Although further details were not given, it is probable that the surviving patients with local failure were treated successfully by RT.

It must be emphasized that the current study excluded patients with adenocarcinoma; these patients are treated with a different CT regimen at our institute. However, the treatment outcome of these patients is considerably worse than that of patients with squamous cell carcinoma (data not shown). Peters et al. [7] reported no survival difference between patients with high-risk adenocarcinoma and those with high-risk squamous cell carcinoma when CCR was used. These findings, along with the fact that more than half of the recurrences in the current study stemmed from adenosquamous carcinoma, suggest that the survival advantage of CT indicated in the current study may apply only to squamous cell carcinoma.

Another issue that must be discussed is complications of adjuvant therapy following surgery. Radical hysterectomy followed by RT is reported to be associated with a relatively high incidence of morbidity [14–16]. Barter et al. [15] reported that 30% of patients treated had serious complications; small bowel obstruction in particular has been one of the major problems of that treatment combination. Data from the current study well reflect the characteristics of our combined therapy. A very low incidence of small bowel obstruction or genitourinary complication was observed. Conversely, a relatively high incidence of locoregional infection was noted. These findings are probably associated with the absence of pelvic RT and the use of postoperative CT. As for leg lymphedema, Soisson et al. [3] reported that the incidence of lymphedema requiring medical therapy was significantly increased from 5.2% in patients treated with surgery alone to 22% in those receiving surgery plus adjuvant pelvic RT. Because there was no control group in our study, we were unable to show an advantage of CT with respect to leg lymphedema, but we do have the impression that CT has little if any adverse effect pertaining to leg lymphedema. Further studies are needed to clarify this point.

In summary, our results suggest the potential role of adjuvant CT alone for patients with cervical cancer. Because of the absence of whole pelvic radiation, this treatment is likely to be advantageous in terms of treatment-related complications. We suggest that CT alone is worth reconsidering as an alternative postoperative therapy for patients with cervical cancer.

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EDITORIAL

Concurrent chemoradiation for cervical cancer: what should we do next?

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Feasibility of concurrent cisplatin use during primary and adjuvant chemoradiation therapy: a phase I study in Japanese patients with cancer of the uterine cervix

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Several randomized trials have demonstrated the therapeutic advantage of concurrent chemoradiotherapy (CCRT) over radiation alone in the treatment of locoregionally advanced uterine cervical cancer.[1–4] Consequently, CCRT is now considered a standard treatment component for patients with uterine cervical cancer. In these trials, cisplatin was used alone or in combination with 5-fluorouracil (5-FU). Rose et al.[2] demonstrated similar survival results and less toxicity with weekly cisplatin compared with moderate-dose cisplatin and 5-FU in a Gynecologic Oncology Group (GOG) study (GOG-120). Based on those results, weekly cisplatin (40 mg/m^2) is now a standard regimen in the United States. However, it should be noted that the average patient age in these studies is younger than that seen in clinical practice in Japan. The Japanese Patterns of Care Study (JPCS) demonstrated that the median age of Japanese cervical cancer patients treated with definitive radiotherapy was 70 years.[5] In contrast, 80%–90% of patients entered in the GOG studies were below 60 years of age.[2–4] Therefore, an original prospective clinical study of CCRT for Japanese patients has been encouraged to assess the feasibility and toxicity of weekly cisplatin at 40 mg/m^2.

In this issue of the *International Journal of Clinical Oncology*, Watanabe et al.[6] report the results of a phase I study of CCRT with single-agent cisplatin in Japanese patients with cervical cancer. They designed two dose-escalation programs for weekly and monthly schedules. Dose-limiting toxicities (DLTs) were investigated separately for both definitive and postoperative settings. Their DLT criteria were designed somewhat similarly to those of recent GOG phase I studies. Treatment delay (i.e., radiotherapy and chemotherapy) of greater than 7 days due to toxicity was defined as a DLT. The investigators observed that the two patients in the definitive CCRT arm and two of the three in the postoperative CCRT arm experienced DLT at the dose level of 40 mg/m^2 (maximum tolerated dose; MTD). Therefore, they recommended a cisplatin dose of 30 mg/m^2 for the weekly schedule. Similarly, they concluded that 75 mg/m^2 should be the recommended dose for the monthly schedule. From these results, they concluded that weekly cisplatin at a dose of 40 mg/m^2 was not feasible for Japanese patients.

To my knowledge, the GOG has not officially performed a phase I/II study of CCRT with weekly cisplatin at a dose of 40 mg/m^2. Therefore, there are no feasibility data for this protocol evaluated by standard DLT criteria, as Watanabe et al.[6] stated in their report. Keys et al.,[3] in GOG-123, showed that 90% of patients were able to receive four or more courses of cisplatin. Similarly, Rose et al.[2] reported that, in GOG-120, four or more courses could be delivered in over 90% of patients and that nearly half of all patients received all the planned courses (six courses) of cisplatin. However, these studies[2,3] did not describe the details or the number of patients who required treatment modification and/or treatment delay, especially in regard to cisplatin administration. As mentioned above, Watanabe et al.[6] have now stated explicitly that more than a 7-day treatment delay constitutes a DLT. Can we not conclude that 8–14 days of delay in cisplatin administration is clinically acceptable in CCRT? Watanabe et al.[6] reported that all patients with DLT experienced granulocytopenia on the day of the planned fourth cycle of cisplatin. If further waiting had been allowed for these patients, the fourth cycle might have been safely given, and this phase I study could have reached a different conclusion. Ohno et al.[7] reported another Japanese phase I study, from the National Institute of Radiological Sciences in Japan. They concluded that weekly cisplatin at 40 mg/m^2 was feasible for Japanese patients. In the Ohno study, a longer treatment delay was allowed; namely, 2 weeks for radiotherapy and 3 weeks for chemotherapy. It should be noted that these authors reported that four of five patients who developed DLT were able to receive the full course of radiotherapy without interruption. In their report, Watanabe et al.[6] also showed that most patients were able to receive the full dose of radiation despite developing DLT.

Regrettably, in their current article, Watanabe et al. did not provide a detailed toxicity profile. Table 1 shows the toxicities that have been reported for CCRT using weekly cisplatin at 40 mg/m^2. The article by Ikushima et al.[8] reports retrospective toxicity data for Japanese patients with cervical cancer who were given concurrent weekly cisplatin and radiotherapy. These authors decided to determine cisplatin

Table 1. Acute toxicity (grade 3 or more) of CCRT using weekly cisplatin at 40 mg/m^2

Author (study)	Year	No. of patients	Toxicity (grade 3/4) %			
			Hematological	Leukopenia	Thrombocytopenia	Gastrointestinal
Rose[2] (GOG-120)	1999	176	–	21/2	2/0	8/4
Keys[3] (GOG-123)	1999	183	18/3	–	–	9/5
Pearcey[10]	2002	127	6/0	–	–	11/5
Serkies[9]	2004	112	–	4/2	0	4/2[a]
Ohno[7]	2005	6	–	83/0	0	16/0
Ikushima[8]	2006	11	91/9	–	–	9/0

[a] Nausea/vomiting

dose according to patient age, with 40 mg/m^2 the dose for younger patients (under 65 years) and 30 mg/m^2 for older patients (65 years or over). They observed that all 11 patients treated with 40 mg/m^2 cisplatin developed grade 3 or greater hematological toxicity. In contrast to these Japanese series, severe hematologic toxicities have been reported to be less frequent in studies conducted in North America and Europe.[2,3,9,10] In Poland, Serkies et al.[9] reported data, from their routine clinical practice, on patient compliance and an acute toxicity profile for CCRT including weekly 40 mg/m^2 cisplatin. Seventy-four percent of their patients with cervical cancer received at least four cycles of cisplatin. They showed that nearly 40% of patients who did not receive the five planned cycles had reasons other than toxicity, such as delayed administration of the first cycle of chemotherapy. They reported that only 5% of patients experienced grade 3 or 4 leukopenia.

On the basis of these findings, what should we do next in CCRT for cervical cancer? I have concluded that a new phase I study seeking an optimal weekly cisplatin dose would have little value. It is important to note that a survival advantage has been demonstrated with cisplatin at the very dose of 40 mg/m^2, but not at a compromised lower dose. On the other hand, it is true that Japanese patients have experienced severe hematological toxicity more frequently than patients in North America and Europe. However, life-threatening toxicity has been uncommon, even in Japanese patients; most importantly, radiotherapy has rarely been interrupted by toxicities. Thus, I believe we should conduct a proper phase II study of CCRT with weekly cisplatin at 40 mg/m^2 for Japanese patients, to determine its toxicity profile and survival outcome. In designing the trial, a treatment modification rule for cisplatin administration should be carefully planned. For this purpose, a detailed description of supportive treatment, such as the use of granulocyte-colony-stimulating factor (G-CSF) should be included in the protocol.

In addition to the scheduling of chemotherapy, the radiotherapy method is another important problem to be investigated in a future trial of CCRT for cervical cancer. There are several differences between the United States and Japan in the radiotherapy methods used. The most notable differences are in the dose rates of intracavitary brachytherapy (ICBT) and the total dose of radiotherapy. Although a National Cancer Institute of Canada (NCIC) study[10] employed not only low-dose-rate (LDR) but also high-dose-rate (HDR) and medium-dose-rate (MDR) ICBT, all randomized studies from the United States have only utilized LDR.[1–4] In contrast, almost all patients in Japan have been treated with HDR-ICBT.[5] Therefore, it should be investigated whether CCRT with HDR-ICBT leads to the same favorable outcome and acceptable toxicity as those demonstrated in earlier randomized studies utilizing LDR-ICBT. In addition, a large variance between the United States and Japan in the total radiotherapy dose has been identified.[11] This is another reason to conduct a prospective phase II study using weekly cisplatin with HDR-ICBT in Japan. Trials of several new chemotherapeutic regimens for CCRT are now underway. Baseline CCRT data with a "standard chemotherapeutic regimen" obtained with Japanese patients will be essential to make proper comparisons with investigational CCRT regimens in future.

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Frequency and characteristics of isolated para-aortic lymph node recurrence in patients with uterine cervical carcinoma in Japan: A multi-institutional study

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Abstract

Objective. In most cases of uterine cervical carcinoma recurrence, the first site of distant metastasis or recurrence is reported to be the para-aortic region. Some reports have demonstrated that, in cases of isolated para-aortic lymph node recurrence treated by radiation therapy, patients survived for a long period, which suggests that isolated para-aortic lymph node recurrence in uterine cervical carcinoma is a regional disease rather than systemic disease. Determining the predictive characteristics of isolated para-aortic lymph node recurrence in patients at the time of the initial treatment for primary uterine cervical carcinoma is important, so we conducted the current multi-institutional study.

Patients and methods. Patients ($n=3137$) with uterine cervical carcinoma of stages Ia to IVa were treated in twelve Japanese hospitals between 1994 and 2003. The current study investigated the frequency and characteristics of patients with isolated para-aortic lymph node recurrence as well as the characteristics of clinical stage, histopathology, serum squamous cell carcinoma antigen level, the treatment method at the initial treatment, the duration between the initial treatment and the recurrence, and the serum squamous cell carcinoma antigen level at the recurrence.

Results. Of the 3137 patients with uterine cervical carcinoma in stages Ia–IVa, 67 (2.1%) experienced recurrence in isolated para-aortic lymph nodes. Stratified by clinical stage, none of the 613 patients with stage Ia experienced recurrence in isolated para-aortic lymph nodes. However, recurrence was experienced by 14 (1.4%) of the 966 patients with stage Ib, 7 (3.5%) of the 199 patients with stage IIa, 14 (2.3%) of the 613 patients with stage IIb, 1 (2.1%) of the 48 patients with stage IIIa, 26 (4.6%) of the 538 patients with stage IIIb, and 5 (5%) of the 100 patients with stage IVa. The mean duration time between the initial treatment and isolated para-aortic recurrence was 20 months (range, 2–49 months). The correlations between duration time and the clinico-pathological factors (clinical stage, histopathology, serum squamous cell carcinoma antigen level, and treatment method) at the initial treatment were investigated. No statistically significant factors have been revealed in the current study.

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