Association of PTEN mutation with HPV-negative adenocarcinoma of the uterine cervix

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Abstract

Serous, mucinous, endometrioid, and clear cell adenocarcinomas arise from reproductive organs of mullerian origin. Although the mutation of PTEN, a tumor suppressor, is known to be involved in tumorigenesis of endometrioid adenocarcinomas of the endometrium and ovary, the role of PTEN alteration in endometrioid adenocarcinoma of the cervix remains to be investigated. To elucidate the molecular pathogenesis of cervical adenocarcinoma and adenosquamous carcinoma, and in particular to examine the potential role of PTEN mutation in endometrioid-type cancer of the cervix, we analyzed 32 cervical adeno- or adenosquamous carcinomas (8 endometrioid adenocarcinomas, 14 mucinous adenocarcinomas and 10 adenosquamous carcinomas) for PTEN mutations and HPV infections. PTEN mutation was detected in 2 of 8 (25.0%) endometrioid cases, 2 of 14 (14.3%) mucinous cases, and none of 10 (0%) adenosquamous cases. HPV DNA was detected in 11 out of 18 (61.1%) PTEN wild-type adenocarcinomas and 8 out of 10 (80.0%) adenosquamous carcinomas. Among 11 HPV-negative adenocarcinomas, 40.0% (2/5) endometrioid cases and 33.3% (2/6) mucinous cases were shown to be PTEN mutated, while no cases (0/21) were PTEN-mutant in the remainder (i.e. adenosquamous carcinomas and HPV-positive adenocarcinomas). The current observations suggest that PTEN mutation is frequently detected in HPV-negative adenocarcinomas of the cervix and the most prevalent occurrence of PTEN mutation in endometrioid subtype is keeping with endometrial and ovarian carcinomas.
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Keywords: PTEN; Mutation; Cervical Adenocarcinoma; HPV

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1. Introduction

Tumor suppressor gene PTEN was identified on chromosome 10q23.3, the region of which is

homozygously deleted in multiple human malignancies [1,2]. Germ-line mutations in PTEN were found in patients with autosomal dominant cancer predisposition syndromes: Cowden disease, Lhermitte-Duclos disease, and Bannayan–Zonana syndrome [3,4]. Somatic mutations and deletions in PTEN were reported in many types of sporadic tumors, including endometrial cancers [5–7], glioblastomas [1,2], prostate cancers [8], and melanomas [9]. PTEN product is thought to contribute to tumorigenesis through induction of apoptosis and cell cycle arrest by antagonizing PI3K/Akt signaling pathway, and also regulate cell adhesion and migration through interactions with focal adhesion kinase [10].

Serous, mucinous, endometrioid, and clear cell adenocarcinomas are derived from reproductive organs of mullerian origin, i.e. ovary, endometrium and cervix, although the incidence of each type of adenocarcinoma is · different according to the organs. Serous tumor is the most common type in ovarian adenocarcinoma, endometrioid tumor in endometrial adenocarcinoma, and mucinous tumor in cervical adenocarcinoma. Endometrioid-type tumor accounts for more than 80% of endometrial carcinomas and 10–20% of ovarian carcinomas. Approximately, 10% of cervical carcinomas are pure adenocarcinomas, 20–30% of which are of endometrioid type. Mutation of the PTEN gene is reported to be detected in 34–55% of endometrial carcinomas and associated with endometrioid histology and favorable survival [5–7,11,12]. PTEN is also mutated in 20% of ovarian endometrioid adenocarcinomas [13,14]. As regards cervical carcinoma, loss of heterozygosity (LOH) of markers on chromosome arm 10q is observed frequently, but PTEN mutation is reportedly rare in cervical squamous cell carcinomas [15–17]. However, the incidence of PTEN mutation in cervical adenocarcinoma is unknown.

Most cervical cancers harbor HPV DNA of high-risk type expressing E6 and E7 oncoporteins [18]. The E6 and E7 oncoporteins are thought to play a crucial role in the cervical carcinogenesis by their interactions with the cellular tumor-suppressor proteins p53 and Rb, respectively: E7 binds and inactivates Rb [19]; E6 binds to p53 and induces its degradation through the ubiquitin pathway [20,21]. HPV DNA is reported to be detected in more than 90% of cervical

squamous cell carcinomas, whereas the incidence of HPV infection in cervical adenocarcinoma in previous reports varies from 40 to 80% [22–24]. HPV-18, which is detected in only 10–20% of squamous cell carcinomas, is found in more than 50% of adenocarcinomas [23,25]. Cervical adenocarcinoma and adenosquamous carcinoma are reported to have a poorer prognosis than cervical squamous cell carcinoma, presumably due to the tendency to grow endophytically and, therefore, to be detected at an advanced stage [26].

To characterize molecular abnormalities of cervical adenocarcinoma and adenosquamous carcinoma, and in particular to identify the potential role of PTEN alteration in cervical endometrioid adenocarcinoma, we analyzed 32 adeno- or adenosquamous carcinomas of the cervix for the presence of PTEN mutations and also for HPV infections. Our findings suggest that PTEN mutation contributes to the tumorigenesis of HPV-negative endometrioid adenocarcinomas of the cervix, as is seen with other organs of mullerian origin, i.e. the endometrium and ovary. Additionally, the current study demonstrates that infection with HPV of high-risk type is playing a major role in the development of adenosquamous carcinomas and PTEN wild-type adenocarcinomas of the cervix.

2. Materials and methods

2.1. Patients and samples

Snap-frozen tumor samples were obtained from 32 Japanese patients who underwent treatment for primary cervical adenocarcinomas and adenosquamous carcinomas at five hospitals (University of Tokyo Hospital, National Cancer Center Hospital, Tokyo Metropolitan Komagome Hospital, Saitama Cancer Center Hospital, and Kinki University Hospital) between 1989 and 2003. Distinction between primary cervical carcinomas and cervical involvement of endometrial carcinomas was determined by the location of main tumor in surgical specimens. Confusing cases were excluded from our study. All patients provided informed consent for the research use of their samples. Cellular DNA was extracted by

a standard sodium dodecyl sulfate (SDS)-proteinase K procedure.

2.2. Detection and typing of HPV

The presence and type of HPV were determined by a PCR-based assay using the consensus primers for the HPV L1 region as described previously [27]. Each amplified product was electrophoresed through a 4% agarose gel, stained with ethidium bromide, and viewed under ultraviolet light. HPV types were identified on the basis of restriction fragment length polymorphism [27]. This assay has been shown to identify at least 26 genital HPVs.

2.3. PCR amplification, SSCP analysis and DNA sequencing

The nine exons of the PTEN gene were amplified using 11 intron-based primer pairs as described previously [28]. SSCP analyses and direct sequencing were performed with slight modification to the method reported by Soong and Iacopetta [29]. Gels were stained with fluorescent dye (SyBR Green II, TaKaRa, Japan) and scanned by a Fluorimager (Molecular Dynamics, Sunnyvale, CA). Aberrant bands revealed by SSCP analysis were excised, purified, and sequenced with an ABI 377 Autosequencer (Perkin–Elmer, Foster City, CA).

3. Results

We analyzed 32 primary cervical adeno- or adenosquamous carcinomas for PTEN alterations and HPV infections. The age of patients ranged from 31 to 78 years. Among 32 cases, 14 were mucinous adenocarcinomas, 10 adenosquamous carcinomas, and 8 endometrioid adenocarcinomas (Table 1). FIGO Staging was as follows: 18, stage I; 12, stage II; 2, stage III (Table 1).

PTEN mutation was detected in 2 of 8 (25.0%) endometrioid cases, 2 of 14 (14.3%) mucinous cases, and none of 10 (0%) adenosquamous cases (Table 1). All of the four PTEN-mutated cases were HPV-negative. Among 11 HPV-negative adenocarcinomas, 40.0% (2/5) endometrioid cases and 33.3% (2/6) mucinous cases were shown to be PTEN mutated,

whereas no cases (0/21) were PTEN-mutant in adenosquamous carcinomas or HPV-positive adenocarcinomas (Table 1). All of the four mutations in PTEN led to the generation of truncated proteins: three were frameshift mutations and one was a nonsense mutation. Two mutations were located in exon 7, one in exon 5, and one in exon 9.

HPV infection was detected in 8 of 10 (80.0%) adenosquamous carcinomas, 8 of 14 (57.1%) mucinous adenocarcinomas, and 3 of 8 (37.5%) endometrioid adenocarcinomas (Table 1). Among 18 PTEN wild-type adenocarcinomas, 11 cases (61.1%) were

Table 1
Details of primary cervical adenocarcinomas and adenosquamous carcinomas

Case	Age	Stage	Histotype	HPV type	PTEN mutation
1	43	IB	E	18	WT
2	43	IB	E	18	WT
3	62	IIA	E	18	WT
4	53	IB	E	Negative	WT
5	47	IB	E	Negative	WT
6	42	IIIB	E	Negative	WT
7	31	IB	E	Negative	233Arg > Stop
8	49	IIB	E	Negative	800delA
9	39	IIB	M	18	WT
10	55	IIA	M	18	WT
11	36	IB	M	18	WT
12	41	IIB	M	18	WT
13	44	IB	M	18	WT
14	45	IIA	M	16	WT
15	43	IB	M	16	WT
16	63	IB	M	16	WT
17	54	IB	M	Negative	WT
18	48	IIB	M	Negative	WT
19	46	IIB	M	Negative	WT
20	49	IB	M	Negative	WT
21	78	IIB	M	Negative	415delTATT
22	67	IB	M	Negative	1038del16bp
23	49	IIB	AS	18	WT
24	45	IB	AS	18	WT
25	42	IB	AS	18	WT
26	52	IIA	AS	16	WT
27	46	IB	AS	16	WT
28	61	IB	AS	16	WT
29	40	IB	AS	16	WT
30	59	IIIB	AS	58	WT
31	52	IIB	AS	Negative	WT
32	62	IB	AS	Negative	WT

E, endometrioid adenocarcinoma; M, mucinous adenocarcinoma; AS, adenosquamous carcinoma.

shown to be HPV-positive. Out of 19 HPV-positive cases, 11 (57.9%) had HPV-18, 7 (36.8%) had HPV-16, and one (5.3%) had HPV-58.

4. Discussion

Although LOH on chromosome arm 10q is observed in 25–28% of cervical carcinomas, including squamous cell carcinomas and adenocarcinomas [15,16], mutation of the PTEN gene, which is located on 10q23.3, was reported to be rare in cervical squamous cell carcinomas [17]. However, the incidence of PTEN mutation in cervical adenocarcinoma is unknown yet. The current study identified mutant PTEN in 40.0% (2/5) of HPV-negative endometrioid adenocarcinomas and 33.3% (2/6) of HPV-negative mucinous adenocarcinomas, whereas no cases (0/21) were found to be PTEN-mutated in the remainder. PTEN mutation was significantly associated with HPV-negative adenocarcinomas ($P = 0.009$ by Fisher's exact test) and the most prevalent occurrence of PTEN mutation was observed in endometrioid subtype (25.0%, Table 1). These findings suggest that PTEN mutation may be playing an important role in the pathogenesis of HPV-negative endometrioid adenocarcinoma of the cervix. According to the recent study on cervical adenocarcinoma by Tsuda et al. [30], endometrioid-type tumor frequently showed LOH on chromosome 10q (43%), which is in line with our current finding. PTEN mutation in endometrial carcinoma is reported to be found in 37–62% of endometrioid adenocarcinomas [5,11]; PTEN mutation in ovarian carcinoma is identified in 20–21% of endometrioid adenocarcinomas [13,14]. Adding our data to these previous observations, it is suggested that PTEN mutation contributes to endometrioid carcinogenesis from epithelium of mullerian origin, including cervix as well as endometrium and ovary.

An aggressive phenotype in some types of tumors including glioma and prostate cancer is reported to be associated with alteration in the PTEN gene [31,32], while some reports have suggested that PTEN mutation correlates with favorable survival of patients with endometrial cancer [11,12]. We previously demonstrated that mutational site on the PTEN gene had prognostic impact in endometrial carcinoma [28].

Harima et al. have recently reported that mutation of the PTEN gene in advanced cervical cancer correlates with tumor progression and poor outcome after radiotherapy [33]. To investigate the association between status or mutational site of the PTEN gene and prognosis of cervical adenocarcinoma, a larger group of samples is needed to be examined.

HPV infection was detected in 8 out of 10 (80.0%) adenosquamous carcinomas and 11 out of 18 (61.1%) PTEN wild-type adenocarcinomas. Among 19 HPV-positive cases, HPV-18 was the dominant type (57.9%). These facts suggest that HPV infection is playing a major role in tumorigenesis of adenosquamous carcinoma and PTEN wild-type adenocarcinoma of the cervix, and that HPV-18 is the most prevalent type in these tumors. Although many findings in the literature indicate that HPV-16 predominates in squamous cell carcinomas and HPV-18 predominates in adenocarcinomas [23,25], the molecular mechanism of this phenomenon remains not identified. Cervical squamous cell carcinoma and adenocarcinoma are considered to arise from squamous metaplastic cells in the ectocervix and columnar cells in the endocervix, respectively. Hence, there is a possibility that different HPV type may possess either different ability to immortalize or different binding affinity to each epithelial cell type in the cervix. Some studies have shown that a transcription factor, C/EBP beta, is an important regulator of activity of HPV-18 URR (upstream regulatory region), which controls cell type-specific expression of E6 and E7 oncoproteins [34,35]. However, further molecular researches are needed to clarify this issue.

In summary, we demonstrate here that PTEN mutation is frequently detected in HPV-negative adenocarcinomas arising from the cervix, whereas infection with oncogenic types of HPV is associated with most of adenosquamous carcinomas and PTEN wild-type adenocarcinomas, implicating that either PTEN alteration or HPV infection may have a causal role in the pathogenesis of cervical adenocarcinoma. We believe that further analysis of molecular alteration in cervical adenocarcinoma and adenosquamous carcinoma will help elucidate the molecular–biological characteristics and behavior of mullerian-origin neoplasias, and also give great benefit to patients with these more aggressive subtypes of cervical carcinoma.

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doi:10.1016/j.ijrobp.2004.02.023

ELSEVIER

CLINICAL INVESTIGATION

USE OF THE SMALL PELVIC FIELD INSTEAD OF THE CLASSIC WHOLE PELVIC FIELD IN POSTOPERATIVE RADIOTHERAPY FOR CERVICAL CANCER: REDUCTION OF ADVERSE EVENTS

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Purpose: We examined whether use of small pelvic (SP) field encompassing only the pericervical regions and upper stream lymphatic will reduce the adverse events that occur with classic whole pelvic (WP) field, in postoperative radiotherapy (RT) for cervical cancer.
Methods and Material: This retrospective study included 72 patients treated with SP field (SP group) used specifically for node-negative status and 46 patients treated with WP field (WP group) used conventionally for node-positive status. Total dose was 50.0 or 50.4 Gy at 2.0 or 1.8 Gy per fraction. Acute adverse events (nausea, diarrhea, cystitis, and leukopenia) and late adverse events (lymphedema, cystitis, ileus, and diarrhea) were graded according to the Common Toxicity Criteria and compared between groups.
Results: Diarrhea (Grades 2–3) and leukopenia (Grades 1–3) occurred significantly more often in WP group (32.4% and 80.5%, respectively) than in SP group (9.2% and 52.2%, respectively). Among the late events, lymphedema occurred most often overall (5-year rate: SP, 47.0%; WP, 49.1%). Only ileus occurred at a significantly higher rate in The WP group than in SP group (5-year rate: 16.2% vs. 3.2%).
Conclusions: Use of the SP field tailored for node-negative status was suggested to reduce adverse events involving the intestine and hemopoietic system. © 2004 Elsevier Inc.

Radiation toxicity, Treated volume, Target volume, Pelvic control.

INTRODUCTION

In the treatment of early-stage cervical cancer, pelvic radiotherapy (RT) may be used as postoperative adjuvant therapy for patients with pathologic risk factors for recurrence (1–5), although the risk of morbidity is heightened by bimodal treatment (6–8). Major pathologic risk factors include lymph node metastasis, deep stromal invasion, parametrial extension, large tumor, and compromised surgical margins. Of these risk factors, lymph node metastasis differs from the others in terms of the recurrence pattern. Lymph node metastasis is associated with both extrapelvic metastasis and intrapelvic recurrence along the lymphatic channels. The other factors, which imply subclinical disease left behind contiguous to the cervical tumor, predict pelvic recurrence at pericervical regions. Despite this difference in implications, the classic whole pelvic (WP) field that covers both pelvic lymphatic channels and pericervical regions is commonly used in most applications of postoperative RT. Mindful of the difference in regions affected by the various risk factors, we have carefully used a small pelvic (SP) field that covers only pericervical regions to treat high-risk, node-

negative patients since 1993. Logically, use of the SP field should reduce treatment-related morbidity without compromising control of pelvic disease. We have elsewhere reported pelvic disease control and overall disease control for cervical squamous cell carcinoma patients treated postoperatively with SP or WP field RT (9). The 5-year pelvic disease control rate in high risk, node-negative patients treated with SP field RT ($n = 42$, 93%) did not differ significantly from that in node-positive patients treated with WP field RT ($n = 42$, 90%), although the overall 5-year disease-free rate was significantly lower for the node-positive patients (61%) than for the node-negative patients (92%) owing to extrapelvic recurrence. In the present study, we retrospectively investigated whether SP field RT reduces the incidence of adverse events in high-risk, node-negative patients.

METHODS AND MATERIALS

Between 1993 and 2001, we treated 145 patients with cervical cancer by postoperative RT after primary surgery.

Pathologic risk factors included in our postoperative RT indication criteria were lymph node metastasis, unknown nodal status, deep stromal invasion ($\geq$ two thirds of the stromal thickness), parametrial extension, and positive or close (< 5 mm) surgical margins. Of the 145 patients, 118 were eligible for the present study. Eligible patients were those who underwent extended radical hysterectomy and bilateral pelvic lymphadenectomy that left no macroscopic disease ($n = 113$) and those who underwent total hysterectomy without pelvic lymphadenectomy for clinical T1a disease that was shown pathologically to be T1b disease ($n = 5$). Patients considered ineligible were those who underwent chemotherapy before or during RT, those who were treated by RT with an extended field that encompassed the para-aortic nodes, those who were treated by four-field irradiation after 2000 to reduce the treated volume compared with by two-opposed field irradiation, and those who had macroscopic disease left behind requiring definitive RT. Eligible patients ranged in age from 19 to 74 years (median 46). Pathologic T classifications according to the TNM classification system (International Union Against Cancer, 1997) included T1b1 ($n = 45$), T1b2 ($n = 25$), T2a ($n = 15$), and T2b ($n = 33$). Histologic types of tumor were squamous cell carcinoma ($n = 100$), adenocarcinoma ($n = 13$), adenosquamous carcinoma ($n = 3$), adenoid basal carcinoma ($n = 1$), and carcinoid ($n = 1$).

Postoperative RT was performed by 10-MV X-ray beams delivered through anteroposteriorly opposed portals. The SP field was used for 72 patients: 71 node-negative patients and 1 elderly node-positive patient. The WP field was used for 46 patients: 34 node-positive patients, 5 unknown-nodal-status patients, and 7 node-negative patients. Fields were set with a conventional X-ray simulator. The SP field, normally 14 cm by 10 cm, covered the pericervical regions of the upper half of the vagina, the retrovesical and prerectal regions, and the parametrial stumps including the lateral lymphatic channels. The WP field, normally 16 cm by 18 cm, encompassed the upper half of the vagina caudally, the parametrial stumps and lymphatic channels laterally, and the lymphatic channels up to the level of the L4–L5 interface (common iliac nodes). Thus, the rectum, bladder, and bilateral external and internal lymphatic channels were included in both the SP and WP field, but the sigmoid colon, a larger volume of small intestine, and bone marrow were included in the WP field than in the SP field. The prescribed total dose was 50.4 or 50.0 Gy at 1.8 or 2.0 Gy per fraction, 5 fractions per week, for both types of RT field. Therefore, the bladder dose-volume was considered identical with both types of RT field.

Sixteen patients underwent boost RT to compromised surgical margins by means of high-dose-rate intracavitary RT to the vagina ($n = 9$) or external RT to the vagina ($n = 3$) or parametrium ($n = 4$). The boost dose by intracavitary RT was 10.0 or 20.0 Gy at 5-mm depth of the vaginal stump in one or two applications, and the boost dose by external RT ranged from 10.0 to 16.0 Gy at 2.0 Gy per fraction, 5 fractions per week. Irradiation was done while the urinary

bladder was full so that the intestine would be pushed beyond the treatment region. If a patient showed a persistent adverse event, particularly diarrhea despite use of antilaxatives (loperamide), the fraction was reduced from 2.0 to 1.8 Gy. If the adverse event persisted despite this reduction, RT was suspended until the problem was solved.

Acute adverse events were defined as adverse effects occurring during RT, and late adverse events were defined as those occurring after RT cessation. Acute events included nausea or anorexia, diarrhea, cystitis (dysuria, urinary urgency), and leukopenia. Complete blood counts were determined weekly for inpatients and arbitrarily for outpatients, and leukopenia was evaluated both before and during RT. Late events were lymphedema (leg edema, pubic edema), chronic diarrhea, ileus (small bowel obstruction), and cystitis (retention, incontinence). Adverse events were determined through review of the clinical charts. Daily general status during RT, such as times of bowel moving and urination and amount of oral intake, was detailed in the charts for 103 patients (87.3%) treated as inpatients, and twice-a-week documentation was available for the remaining 15 patients (12.7%) treated as outpatients. After cessation of RT, patients were examined monthly for the first year, every other month for the next year, and every 4–6 months thereafter as long as the clinical course was smooth. The patients were examined by at least one of the authors who paid special attention to edema and ileus; diarrhea and cystitis were recorded if patients complained of them. Events were graded according to the Common Toxicity Criteria proposed by the National Cancer Institute (version 2.0, 1999) (10), as shown in Table 1. The worst status observed during the observation period was used even if status improved over time.

The group of patients treated by SP field RT (SP group) was compared with the group treated by WP field RT (WP group). Differences between the groups in patient characteristics and treatment variables including age, T stage, fraction size, and use of boost RT were analyzed by Student's t test or the chi-square test. The incidence of acute adverse events was compared between groups, and statistical differences were analyzed by chi-square or Fisher's exact test. The incidence of late adverse events was estimated cumulatively by the Kaplan-Meier method. In estimating the incidence of late adverse events, adverse events classified as Grade 1 or higher were counted at the time of occurrence. The data were censored for patients who died or were alive or lost to follow-up if without adverse event at the time of the last follow-up visit. The data for patients who showed recurrence that could cause symptoms resembling adverse events were also censored at the time of diagnosis of recurrence. Statistical difference in the incidence of late adverse events between the groups was evaluated by log-rank test. StatView 5.0 (SAS Institute, Inc., Cary, NC) was used for all statistical analyses. P values of less than 0.05 were considered statistically significant.

Table 1. Common toxicity criteria proposed by the National Cancer Institute

	Grade				
	0	1	2	3	4
Acute adverse event					
Nausea/anorexia	None	Able to eat	Oral intake significantly decreased	No significant intake, requiring i.v. fluids	Requiring feeding tube or parenteral nutrition
Diarrhea	None	Increase of <4 stools/day over pretreatment	Increase of 4–6 stools/day, or nocturnal stools	Increase of ≥7 stools/day or incontinence, or need for parenteral support for dehydration	Physiologic consequences requiring intensive care; hemodynamic collapse
Dysuria	None	Mild symptoms requiring no intervention	Symptoms relieved with therapy	Symptoms not relieved despite therapy	—
Urinary urgency	Normal	Increase in frequency or nocturia up to 2 × normal	Increase >2 × normal but <hourly	Hourly or more with urgency or requiring catheter	—
Leukocytes (total WBC)	WNL	<LLN–3.0 × 10⁹/L	≥2.0–<3.0 × 10⁹/L	≥1.0–<2.0 × 10⁹/L	<1.0 × 10⁹/L
Late adverse event					
Lymphatics	Normal	Mild lymphedema	Moderate lymphedema requiring compression; lymphocyst	Severe lympedema limiting function; lymphocyst requiring surgery	Severe lymphedema limiting function with ulceration
Diarrhea (periodic)	None	Increase of <4 stools/day over pretreatment	Increase of 4–6 stools/day, or nocturnal stools	Increase of ≥7 stools/day or incontinence, or need for parenteral support for dehydration	Physiologic consequences requiring intensive care; hemodynamic collapse
Ileus	None	—	Intermittent, not requiring intervention	Requiring nonsurgical intervention	Requiring surgery
Urinary retention	Normal	Hesitancy or dribbling, but no significant residual urine; retention occurring during the immediate postoperative period	Hesitancy requiring medication or occasional in/out catheterization (<4 × per week), or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	Requiring frequent in/out catheterization (≥4 × per week) or urological intervention (e.g., TURP, suprapubic tube, urethrotomy)	Bladder rupture
Incontinence	None	With coughing, sneezing, etc.	Spontaneous, some control	No control (in the absence of fistula)	—

Abbreviations: WBC = white-blood cells; WNL = within the normal limit; LLN = lower limit of the normal; TURP = transurethral resection of the prostate.

RESULTS

Patient age did not differ significantly between the SP group and the WP group, but T stage and fraction size did differ significantly (Table 2). In the WP group, T2 stage disease predominated, reflecting the relatively high frequency of lymph node metastasis associated with advanced-stage disease. The small 1.8-Gy fraction was used preferentially for WP field irradiation. The use of boost RT did not differ significantly between groups. The observation period after surgery was 2 years or more for 90 patients (76.3%), 3 years or more for 70 (59.3%), and 5 years or more for 41 (24.7%); the median observation period was 45.0 months.

Surgery-induced adverse events appeared before RT in 15 patients (SP group, n = 8; WP group, n = 7). These adverse events included Grade 3 ileus in 5 patients (SP group, n = 2; WP group, n = 3), ureteral injury requiring stenting in 4 (SP group, n = 2; WP group, n = 2), atonic bladder in 3 (SP group, n = 3), retroperitoneal infection in 2 (WP group, n = 2), and Grade 2 leg edema in 1 (SP group, n = 1). Among the surgery-induced events that could be counted as late adverse events, those that occurred temporarily, such as ileus, were counted if they reappeared after RT, but those that persisted, such as urinary symptoms, were counted at the time of RT cessation.

Table 2. Patient age, T stage, and treatment variables in the two treatment groups

	SP (*n* = 72)	WP (*n* = 46)	*p* value
Age: range (median), years	19–74 (46)	26–71 (47)	0.6417
T stage			0.0038
T1b1	31	14	
T1b2	20	5	
T2a	9	6	
T2b	12	21	
Initial fraction size			0.0081
1.8 Gy	9	15	
2.0 Gy	63	31	
Fraction size reduction			0.1054
Yes	11	10	
No	52	21	
Boost irradiation			0.1277
Yes	7	9	
No	65	37	

Abbreviations: SP = group in which small pelvic field radiotherapy was used; WP = group in which whole pelvic field radiotherapy was used.
Numbers are number of patients unless otherwise indicated.

Acute nausea or anorexia was evaluated for all patients. In the analysis of diarrhea and cystitis, 102 patients (SP group, *n* = 65; WP group, *n* = 37) excluding the 16 patients who underwent boost RT were used because it was thought that boost RT could increase these symptoms. Complete blood counts before RT were available for 110 patients (SP group, *n* = 69; WP group, *n* = 41), and complete counts during RT were available for 108 patients (SP group, *n* = 67; WP group, *n* = 41). The incidences of diarrhea and leukopenia were greater than those of nausea or anorexia and cystitis (Table 3). Overall, diarrhea and leukopenia reached Grade 2 or 3 relatively often, whereas cystitis and nausea or anorexia never reached Grade 2 or 3. No acute event reached Grade 4. Diarrhea and leukopenia occurred significantly more often in the WP group than in the SP group (Figs. 1 and 2); the between-group difference in the incidence of diarrhea was significant if Grade 0 and 1 were combined and compared against Grade 2 and 3 combined (Fig. 1). In contrast, cystitis occurred significantly more often in the SP group than in the WP group owing to
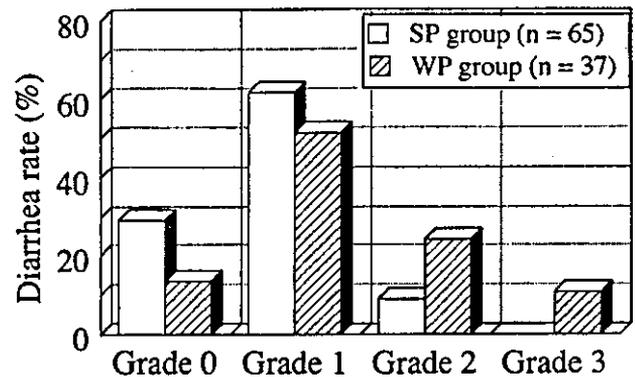

Fig. 1. Occurrence of diarrhea, an acute adverse event, according to grade and treatment group. SP group = patients treated with small pelvic field radiotherapy; WP group = patients treated with whole pelvic field radiotherapy.

preferential occurrence of surgery-induced adverse events in the SP group. There was no significant between-group difference in the incidence of nausea or anorexia.

In the analysis of late adverse events, the 16 patients undergoing boost RT were excluded and analyzed separately. Another 5 patients who did not undergo pelvic lymphadenectomy were excluded from the analysis of lymphedema. Among the late adverse events, lymphedema occurred most often (Table 4, Fig. 3); none of the 5 patients without pelvic lymphadenectomy showed lymphedema. Lymphocyst infection or lymphangitis was found in 15 patients (SP group, *n* = 12; WP group, *n* = 3). No late adverse event reached Grade 4. Ileus reached Grade 3 in 6 patients (SP group, *n* = 1; WP group, *n* = 5) and in another 2 boost RT patients (SP group, *n* = 1; WP group, *n* = 1) and lymphedema reached Grade 3 in 1 patient (WP group, *n* = 1). The incidence of Grade 3 events was significantly higher in the WP group than in the SP group (*p* = 0.0021). Ileus was the only late event that differed significantly in incidence between the groups (Fig. 4). The incidence of adverse events tended to be increase in patients undergoing boost RT.

Further analysis was done to determine whether lymphedema, which occurred equally often in both treatment groups, was influenced by fraction size. For this anal-

Table 3. Incidence of acute adverse events in relation to grade per treatment group

	SP		WP		*p* Value (SP vs WP)	
	Grade 1–3	Grade 2–3	Grade 1–3	Grade 2–3	Grade 1–3	Grade 2–3
Nausea/anorexia (*n* = 118)	34.7%	0.0%	43.5%	0.0%	0.3396	—
Diarrhea (*n* = 102)	72.3%	9.2%	86.5%	32.4%	0.0995	0.0031
Cystitis (dysuria/urgency, *n* = 102)	26.2%	0.0%	2.7%	0.0%	0.0028	—
Leukopenia during RT (*n* = 108)	52.2%	14.9%	80.5%	14.6%	0.0032	0.9670
PreRT leukopenia (*n* = 110)	15.9%	5.8%	2.4%	0.0%	0.0298	0.2947

Abbreviations: SP = group in which small pelvic field radiotherapy was used; WP = group in which whole pelvic field radiotherapy was used.
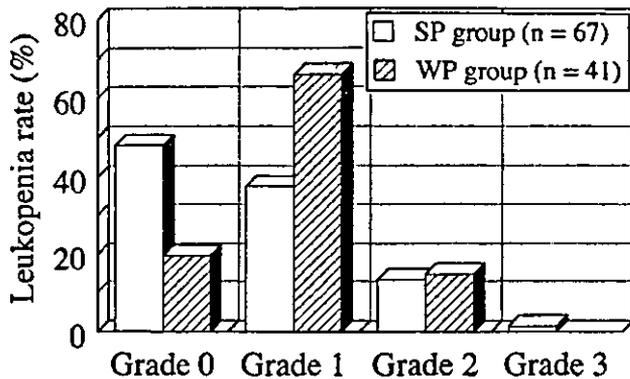No Grade 4 event was identified.

Fig. 2. Occurrence of leukopenia, an acute adverse event, according to grade and treatment group. SP group = patients treated with small pelvic field radiotherapy; WP group = patients treated with whole pelvic field radiotherapy.
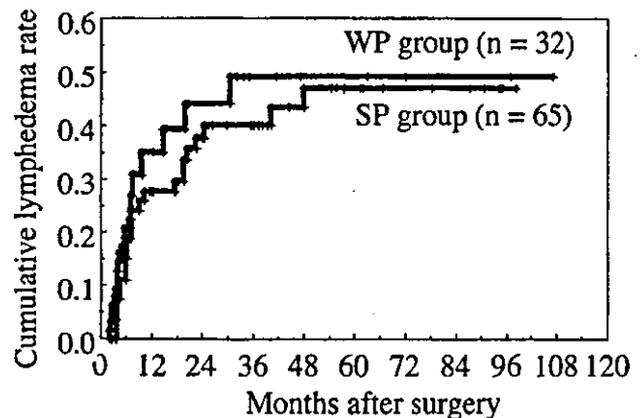

Fig. 3. Cumulative occurrence rate of lymphedema, a late adverse event, according to treatment group. SP group = patients treated with small pelvic field radiotherapy; WP group = patients treated with whole pelvic field radiotherapy.

ysis, patients who did not undergo lymphadenectomy, those who received boost RT, and those in whom the fraction was reduced were excluded; 18 patients treated exclusively with 1.8-Gy fractions (SP group, n = 9; WP group, n = 9) and 60 patients treated exclusively with 2.0 Gy-fractions (SP group, n = 45; WP group, n = 15) were compared. The cumulative incidence of lymphedema tended to be higher with 1.8-Gy fractions (77.3% at 5 years) than with 2.0-Gy fractions (35.0% at 5 years, p = 0.0577); SP group patients were treated with 1.8-Gy fractions significantly more often (p = 0.0438).

DISCUSSION

The occurrence of adverse events relates to the size of the treated volume that involves organs at risk, which volume is defined in the report on the rules of prescribing dose and volume (ICRU report 50) (11), if other conditions such as total radiation dose, fraction size, and surgical stress burden match. The size of the treated volume depends primarily on the planning target volume determined, which volume is also defined in the ICRU report, and secondarily on the radiation technique used. Radiation techniques such as the conventional four-field technique and the recently devised intensity-modulated radiotherapy technique (12, 13) are

useful from the standpoint of tailoring the treated volume to conform to the planning target volume. Ideally, the planning target volume is determined by including the volume where disease exists or is likely to exist and excluding the volume where disease is unlikely to exist. Therefore, the SP field that covers only pericervical regions where disease is likely to exist should be appropriate for node-negative cervical cancer patients, and use of the SP field instead of the classic WP field will contribute to a decrease in adverse events.

Of the acute adverse events we evaluated, diarrhea and leukopenia occurred at significantly lower rates in the SP group than in the WP group. This outcome can be explained simply by the specific reduction of treated volume involving the small bowel and bone marrow. Unexpectedly, however, acute cystitis occurred more frequently in the SP group than in the WP group, despite inclusion of the entire bladder area in the treated volume of both groups. This inconsistency could be attributed to surgery-induced adverse events that happened to have occurred preferentially in the SP group.

Acute adverse events may not be considered as serious as late adverse events because acute events are usually temporary and reversible, whereas late events are apt to be persistent and irreversible. However, patients should be relieved of adverse events as much as possible. In addition to

Table 4. Incidence and cumulative rate of late adverse events per treatment group

	SP (n = 65)		WP (n = 37)		p Value SP vs WP	Boost RT (n = 16)		p Value vs No boost RT
	Incidence	5-year rate	Incidence	5-year rate		Incidence	5-year rate	
Lymphedema (WP, n = 32)	38.5%	47.0%	37.5%	49.1%	0.7534	56.2%	72.5%	0.1570
Diarrhea (periodic)	4.6%	5.7%	5.4%	6.4%	0.7861	6.3%	10.0%	0.8059
Ileus	3.1%	3.2%	13.5%	16.2%	0.0384	12.5%	19.2%	0.4949
Cystitis (retention/incontinence)	18.5%	22.6%	5.4%	6.1%	0.0870	25.0%	26.6%	0.1981

Abbreviations: SP = group in which small pelvic field radiotherapy without boost was used; WP = group in which whole pelvic field radiotherapy without boost was used; RT = radiotherapy.

The cumulative rate was shown at 5-year rate. The p value was calculated for the cumulative rate.
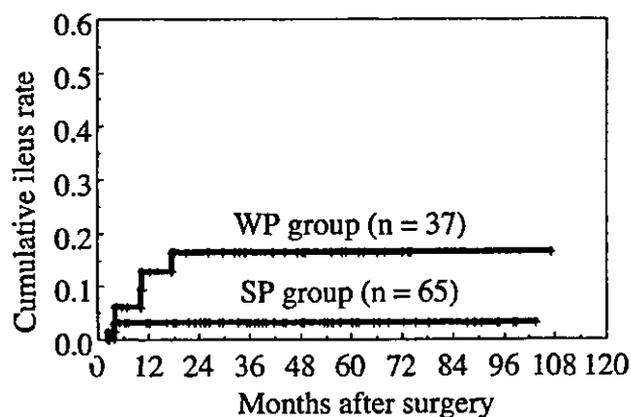
Fig. 4. Cumulative occurrence rate of ileus, a late adverse event, according to treatment group. SP group = patients treated with small pelvic field radiotherapy; WP group = patients treated with whole pelvic field radiotherapy.

reasonable minimization of the target volume, use of a small fraction size (1.8 Gy but not 2.0 Gy) and refined radiation techniques, such as four-field irradiation that we currently use and intensity-modulated radiation therapy, will decrease the incidence and grade of diarrhea.

Fortunately, late Grade 4 adverse events requiring surgical intervention, i.e., so-called severe complications, did not occur in either of our patient groups. Late Grade 3 adverse events, predominantly ileus, occurred in only 8 (6.8%) of the total 118 patients. Barter *et al.* (6) observed severe complications more frequently than we did: 8 (16%) of their 50 patients undergoing radical hysterectomy and postoperative RT showed ileus, which was also the main overall complication. The difference in the incidence of late adverse events may be due to the skill of the treating gynecologists (14). Investigating postoperative RT-related ileus, Montz *et al.* (15) compared the incidence and grade of ileus between 60 patients undergoing radical hysterectomy and 20 patients undergoing radical hysterectomy and postoperative RT, probably with a WP field. They observed that 5% ($n = 3$) of the surgery-alone patients and 20% ($n = 4$) of the postoperative RT patients had Grade 4 ($n = 6$) or Grade 3 ($n = 1$) ileus; this difference was significant. In addition, they observed at surgery that small bowel adhesion involved mainly the distal ileum (15), which will be included frequently in the WP field but rarely in the SP field. Grade 3 ileus occurred more frequently in our WP field RT group than in our SP field RT group. These observations support the theory that postoperative RT heightens the risk of ileus predisposed by surgical treatment in proportion to the volume of small bowel included in the treated volume.

In our present study, the incidence of cystitis, the representative urinary adverse event, could have been underestimated because usual subjective cystitis symptoms can be masked by surgery-induced urinary dysfunction such as incomplete voiding and insensibility to the feeling of fullness. Patients also might not have been aware of residual urine or might have hesitated to report incontinence, which,

like sexual dysfunction, can be a delicate issue. In fact, Ralph *et al.* (16) reported a high incidence of adverse urinary events after performing exhaustive urologic examinations in 48 patients undergoing postoperative RT: impaired spontaneous micturition, 80%; impaired bladder sensation, 73%; incontinence, 52%; urgency, 48%; nocturia, 46%; and urinary tract infection, 29%. Therefore, we conclude that if those patients undergoing urologic examinations had fully reported their symptoms, the recorded incidence of urologic adverse events would have been substantially greater in both of our groups.

Lymphedema was the most notable late adverse event in the present study because it occurred in approximately half of the patients in both groups. Although Grade 1–2 lymphedema may not be serious or life threatening and may not even be counted among late complications, patients suffering from it will feel fettered in their daily activities and may be prevented from continuing with long-standing daily work and leisure routines. A high incidence of lymphedema, like ours, was reported by Chatani *et al.* (17). For 128 patients with T1b–T2b disease, they observed lymphedema at 42% for a 5-year cumulative incidence after postoperative RT with a WP field. Regarding the effect of treated volume on lymphedema, our study showed no significant difference in the cumulative incidence between groups. We attribute this to the fact that our SP field included lateral lymphatic channels as did the WP field. We consider the lymphatic flow to be disturbed primarily by surgery and that radiation exacerbates the flow disturbance; lymphedema rarely occurs in association with definitive RT (18). Lateral lymphatic channels are difficult to exclude from the target volume when T2b disease is treated by postoperative RT because parametrial stumps are in close proximity to the lateral lymphatic channels. It remains unclear whether the fraction size was related to lymphedema.

A simple but certain means to reducing adverse events is to avoid bimodal treatment if identical survival and pelvic control can be achieved by either treatment. Landoni *et al.* (8) conducted a randomized study of T1b–2a cervical cancer patients in which results supported avoiding bimodal treatment. They showed that overall and disease-free survivals were comparable between 169 patients treated by surgery with ($n = 108$) or without ($n = 61$) postoperative RT and 158 patients treated by definitive RT and that the incidence of severe late complications was significantly higher in the surgery group, particularly in the subgroup undergoing postoperative RT. In the United State, the National Institutes of Health has recently provided a consensus statement that the combined use of surgery and RT for patients with T1b–2a cervical cancer should be avoided because combined therapy substantially increases the cost of and morbidity associated with treatment (19). In Japan, however, patients with resectable cervical cancer, including clinical T2b disease, have traditionally been managed primarily by surgery. To justify this traditional treatment policy, particularly for T2b disease, which normally requires

postoperative RT, it will be necessary to compare clinical results between patients treated by combined therapy and those treated by definitive RT alone.

In conclusion, use of the SP field tailored for node-negative status was suggested to reduce adverse events involving the intestine and hemopoietic system, which related deeply to the size of treated volume. Further study is needed to confirm this.

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REVIEW ARTICLE

Kazuo Kuzuya

Chemoradiotherapy for uterine cancer: current status and perspectives

Abstract The conventional local treatment methods (surgery and radiation) for cervical cancer have reached a plateau in terms of survival benefit and, therefore, in this review, new treatment strategies (combined chemotherapy [CT] and local therapy) to overcome the poor prognosis were examined in high-risk groups. The effectiveness of neoadjuvant chemotherapy (NAC) administered prior to radiotherapy (RT) has not been confirmed for any disease stages. But NAC followed by surgery may improve survival in patients with stage Ib2 compared with surgery alone; and in patients with stage Ib2 to IIB compared with RT alone. Five large randomized clinical trials (RCTs) demonstrated a significant survival benefit for patients treated with concurrent chemoradiotherapy (CCRT), using a cisplatin (CDDP)-based regimen, with a 28%–50% relative reduction in the risk of death. In addition, the results of a metaanalysis of 19 RCTs of CCRT (1981–2000) involving 4580 patients showed that CCRT significantly improved overall survival (OS) hazard ratio ([HR] 0.71; $P < 0.0001$), as well as progression-free survival (PFS; HR 0.61; $P < 0.0001$). In line with these results, CCRT is currently recommended as standard therapy for advanced cancer (stage III/ IVA) in the United States. However, there remains much controversy and uncertainty regarding the optimal therapeutic approaches, especially for patients with advanced cancer. Additional RCTs should be conducted to find the optimal CT regimen and RT for Japanese patients, considering acute and late complications, as well as differences in pelvic anatomy, total radiation dose, and RT procedures between Japan and other countries. Evidence obtained from such studies should establish the optimal CCRT treatment protocol and define the patient population (disease stage) that the protocol really benefits.

Introduction

The standard treatment options for cervical cancer are surgery and radiotherapy (RT). In Japan, surgery (radical hysterectomy) has been chosen as the primary treatment for patients with International Federation of Obstetricians and Gynecologists (FIGO) stage I/II disease. Postoperatively, these patients usually receive adjuvant therapy, with external irradiation (if they have poor prognostic factors, such as lymph node metastases, parametrial involvement, deep invasion, and bulky tumor) or with brachytherapy (if they have positive surgical margins of the vagina or have undergone suboptimal resection). For patients with FIGO stage III/IV disease, primary treatment has usually been RT (external irradiation and brachytherapy).

However, there have been no associated improvements in the prognosis of patients at any disease stage; 5-year survival rates for stages I, II, III, and IV patients after initial treatment were 81.9%, 61.8%, 38.1%, and 12.8%, respectively, in 1972 and 83.5%, 63.5%, 39.7%, and 13.1%, respectively, in 1989.[1] The FIGO data from 1993 to 1995[2] also indicate that the prognosis of advanced cervical cancer remains poor, with 5-year survival rates for stages IB, IIB, IIIA, IIIB, IVA, and IVB at 80.7%, 73.3%, 50.5%, 46.4%, 29.6%, and 22.0%, respectively.

These data suggest that the technical advances in each of these conventional local treatment methods (i.e., surgery and RT) have reached a plateau and, therefore, that new treatment strategies are required to overcome the poor prognosis. In this context, in this review, several approaches of combined chemotherapy (CT) and local therapy were examined in high-risk cervical cancer patients. While no effective CT regimens have been established so far for adenocarcinoma, squamous cell carcinoma was reported to be relatively sensitive to some CT regimens. Subsequently, especially since cisplatin (CDDP) has become available,

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CT has been widely incorporated into the treatment for cervical cancer patients, mainly for those with advanced or recurrent disease, in attempts to improve their prognosis.

CT may be incorporated into the initial treatment as neoadjuvant CT, neoadjuvant/adjuvant chemoradiotherapy (CRT), or definitive CRT. This article reviews the current status of CRT, as well as neoadjuvant chemotherapy (NAC), for squamous cell carcinoma of the cervix.

Role of chemotherapy (CT)

The aim of introducing CT into the treatment of cervical cancer, especially of advanced disease, is to improve the prognosis, by controlling not only local disease but also micro-metastases, which may be present in many patients.

CT for untreated patients has so far been investigated in mainly phase II studies, using platinum-based regimens in the neoadjuvant setting; such regimens have produced high response rates, ranging from 42.5% to 100%.[3] Promising regimens that were associated with complete response (CR) rates of more than 20% include bleomycin (BLM) + vincristine (VCR) + mitomycin-c (MMC) + cisplatin [CDDP] (BOMP; 25.5% and 35%), CDDP + 5-fluorouracil (5-FU) (PF; 27%), and CDDP + VCR (PV; 25.9%). Several other regimens were also associated with favorable results in the neoadjuvant setting or in concurrent combination with RT.

Current status of neoadjuvant chemotherapy (NAC)

There are theoretical advantages of using NAC prior to definitive treatment with surgery or RT; NAC may promote the efficacy of definitive treatment on local control by downstaging the tumor adequately before intratumoral blood flow is affected by definitive treatment, and NAC may even contribute to micro-metastasis control. For these reasons, the effectiveness of NAC administered prior to definitive surgery or RT has been actively studied since the 1980s.

NAC followed by RT

Table 1[4-11] presents the outlines of eight major randomized controlled trials (RCTs) comparing NAC followed by RT versus RT alone. These studies enrolled patients with stage IIB to IV disease and used various platinum-based regimens, including CDDP alone and combinations of CDDP with BLM, VCR, MMC, methotrexate, chlorambucil, ifosfamide (IFS), epirubicin, or 5-FU. It was expected that tumor reduction prior to definitive RT would provide a therapeutic advantage in terms of improved radiation dose distribution. However, none of these studies demonstrated a statistically significant survival benefit for patients randomized to the NAC arm, although the survival rate was somewhat higher in the NAC-RT arms in some studies. Instead, some of these studies reported that NAC followed by RT was associated with significantly poor prognosis.[4,8]

A metaanalysis also concluded that NAC administered prior to RT provided no advantages.[12] In this metaanalysis, the superiority of NAC followed by RT over RT alone was found only when CT included CDDP with a dose intensity of 25 mg/m^2 per week or higher and was repeated within 14 days. The lack of the effectiveness of NAC is considered to be due to the development of cross-resistance with the chemotherapeutic agents and RT. To make a definitive conclusion about the role of NAC administered prior to RT, a comparison of NAC followed by RT versus CRT may be required.

NAC followed by surgery

NAC followed by definitive surgery has been studied in comparison with surgery alone, RT alone, or concurrent CRT (CCRT; Table 2).

In a retrospective study involving patients with stage IB2 disease, reported by Serur et al.,[13] there was a trend toward improved survival in patients who received NAC compared with those who received surgery alone, but the difference was not statistically significant. Two other retrospective studies of NAC followed by surgery versus RT alone[14] or CCRT[15] also failed to demonstrate a significant improvement in survival.

Table 1. NAC+RT vs RT in cervical cancer

Author	Stage	CT Regimen	No. of patients	RR (%)	Survival (%) CT+RT vs RT (follow-up)	P
Souhami,[4] 1991	IIIB	BOMP	107	47 vs 32.5 (CR)	23 vs 39 (5-Year)	0.02
Chauvergne,[5] 1993	IIBN1-III	COMeP	151	96 vs 93 (RR)	40 vs 35 (4-Year)	NS
Chiara (GONO),[6] 1994	IIB-III	P	64	78 vs 81 (RR)	59 vs 72 (3-Year)	NS
Kumar,[7] 1994	IIB-IVA	BIP	184	56 vs 61 (RR)	38 vs 36 (4-Year)	NS
Tattersall,[8] 1995	IIB-IVA	EP	260	72 vs 92 (RR)	48 vs 69 (15 Months)	0.02
Sundfor,[9] 1996	IIB-IVA	PF	94	56 vs 61 (CR)	26 Months vs 22 Months (MS) 38 vs 40 (?)	NS
Leborgne,[10] 1997	–	BOP	130	68 vs 95 (RR)	38 vs 49 (? Year)	NS
Symonds,[11] 2000	IIB-IV	MeP	204	–	47 vs 40 (3-Year)	NS

CT, chemotherapy; RT, radiotherapy; RR, response rate; CR, complete response; B, bleomycin; O, vincristine; M, mitomycin; P, cisplatin; C, chlorambucil; Me, methotrexate; I, ifosfamide; E, epirubicin; F, 5-FU; MS, median survival; NS, not significant

Table 2. NAC+surgery vs surgery or RT or CCRT in cervical cancer

Author	Stage	Design	CT Regimen	No. of patients	Survival (%) CT+RT vs RT (follow-up)	P
Serur,[13] 1997	IB2	NAC+S vs S	BMeP	54	80 vs 69 (5 Years)	0.162
Chen,[14] 2001	IB2-IIA	NAC+S vs RT	BOP	58	? vs ? (5 Years)	NS
Duenas-Gonzalez,[15] 2002	IB2-IIIB	NAC+S vs CRT	PGP	127	62 vs 65 (2 Years)	NS
Sardi,[16] 1997	IB	NAC+S±RT vs S±RT	BOP	205	81 vs 66 (8 Years)	< 0.05
Chang,[17] 2000	IB2-IIA	NAC+S vs RT	BOP	120	70 vs 61 (5 Years)	NS
Benedetti-Panici,[18] 2002	IB2-IIB	NAC+S vs RT	P	322	65 vs 46 (5 Years)	0.005

NAC, neoadjuvant chemotherapy; CT, chemotherapy; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; S, surgery; B, bleomycin; O, vincristine; P, cisplatin; Me, methotrexate; G, gemcitabine

On the other hand, there were several reports from RCTs demonstrating the effectiveness of NAC administered prior to surgery.

Sardi et al.[16] reported that NAC using the BOP regimen (BLM + VCR + CDDP), followed by surgery with or without RT was associated with a significant improvement in 8-year survival rate compared with surgery alone or surgery with RT in patients with stage IB disease (81% vs 66%; $P < 0.05$). A subgroup analysis by disease stage also showed an improvement in the 8-year survival rate of stage IB2 patients, with higher significance (80% vs 61%; $P < 0.01$), while there was no significant difference in the survival rate of stage IB1 patients (82% vs 77%; not significant [NS]).

In a study reported by Benedetti-Panici et al.,[18] NAC with CDDP followed by surgery was compared with RT alone in patients with stage IB2 to IIB disease. The 5-year survival rate was significantly higher in the NAC arm (65% vs 46%; $P = 0.005$). This study did not make a comparison with surgery alone.

A small metaanalysis (n = 872), consisting mainly of patients with stage I/II disease, also found a significantly better prognosis for patients treated with NAC followed by surgery compared with those treated with RT alone, with hazard ratios (HRs) for 5-year overall survival (OS) and progression-free survival (PFS) of 0.65 and 0.68, respectively.[19]

In a study reported by Napolitano et al.,[20] NAC using the BOP regimen followed by surgery was compared with surgery or RT alone. NAC was associated with an improvement in 5-year disease-free survival (DFS) but not in 5-year OS for patients with stage IB/IIA disease. For patients with stage IIB to IIIB disease, NAC did not result in an improvement in either 5-year OS or 5-year DFS.

Chang et al.[17] reported a study comparing NAC, using the BOP regimen followed by surgery, with RT alone in patients with IB2 to IIB disease. The 5-year survival rate was higher in the NAC arm, but the difference was not statistically significant (70% vs 61%).

There are two additional similar comparative studies, one in stage IIB patients and one in stage IIIB patients. NAC improved the prognosis in the former study, while negative results were obtained in the latter study.[21,22]

With the above results taken together, the current status of NAC is summarized as follows: (1) The effectiveness of NAC administered prior to definitive RT has not been confirmed for any disease stages; (2) NAC followed by surgery

may improve the survival of patients with stage IB2 disease compared with surgery alone; and (3) NAC followed by surgery may improve the survival of patients with stage IB2 to IIB disease compared with RT alone.

However, the effectiveness of NAC administered prior to surgery has been observed only in small studies and therefore needs to be confirmed by larger studies to compare NAC followed by surgery versus surgery, RT, or CCRT, especially for patients with bulky stage I/II disease. In Japan, an RCT (Japan Clinical Oncology Group [JCOG] 0102) is currently being conducted to assess the efficacy of NAC using the BOMP regimen, followed by definitive surgery with or without RT, in comparison with surgery with or without RT in patients with stage IB2 to IIB disease.

Current status of primary concurrent chemoradiotherapy (CCRT)

One of the theoretical advantages of combining CT with RT is an additive or synergistic antitumor activity, although the mechanism of their interaction remains to be elucidated.[23]

In the 1980s, survival advantages of concurrent treatment with hydroxyurea (HU) and RT over RT alone were reported in some studies. Subsequently, several RCTs, including the following, were conducted to examine the efficacy of CCRT using various regimens.

In a Gynecologic Oncology Group (GOG) trial,[24] 296 patients with stage IIB to IVA disease were randomized to receive HU or misonidazole, concurrently with RT. The 5-year DFS was higher in patients who received HU, but the difference was not statistically significant.

Tseng et al.[25] conducted a study comparing RT combined with concurrent PVB (CDDP + VCR + BLM) versus RT alone in 122 patients with stage IIB to IIIB disease, and reported a higher response rate in the CCRT arm (77% vs 61%). No significant difference was observed for 3-year survival (61.7% vs 64.5%).

Colombo et al.[26] compared RT combined with concurrent FJ (5-FU + carboplatin [CBDCA]) versus RT alone in 56 patients with stage IB2 to IVA disease, but found no significant difference in 5-year survival (66% vs 70%).

In another study, reported by Thomas et al.,[27] 234 patients with stage IB2 to IVA disease were randomized to one of four treatment arms: standard RT alone, standard

Table 3. Large randomized studies of concurrent chemoradiaotherapy in cervical cancer

Author	Stage	Design	RT	CT (mg/m², except for HU)	No. of patients	Survival (%) CT/RT vs RT (follow-up)	P
Whitney,[28] GOG 85, 1999	IIB-IVA PAN (−), Washing cytology (−)	WP+PF×3 vs WP+HU+PAN	IIB:40Gy+Ra III,IVA:WP, 51Gy+Ra III,IV:61Gy	P:50/Day1 F:1000/Days2–5, q 4 Weeks HU:80mg/kg/twice a Week	388	55 vs 43 (8.7 Years)	0.018
Rose,[29] GOG 120, 1999	IIB-IVA PAN (−)	WP+P weekly vs WP+PF+HU vs WP+HU	IIB:40Gy+Ra III,IVA:WP, 51Gy+Ra III,IV:61Gy	P:40/Week for 4 Weeks vs P:50/Day1+F:1000/Days1–4+ HU:2000/2/Week, q 4 weeks vs HU:3000/2/Week for 6 Weeks	176	66 vs 67 vs 50 (3 Years) 81 vs 71 (4 Years)	0.004 0.002
Keys,[30] GOG 123, 1999	IB ≥4cm	WP+P weekly vs WP Adj ATH	WP:45Gy+Ra	P:40/Week for 6 Weeks	369	83 vs 74 (3 Years)	0.008
Morris,[31] RTOG 90-01, 1999	IB-IVA >5cm or PAN (+)	WP+PF×3 vs WP+PAN	WP:45Gy PAN:45Gy	P:75/Day1 F:1000/Days2–5, q 3 Weeks	386	83 vs 58 (5 Years)	0.004
Peters,[32] SWOG 8797, 2000	IA2-IIA Postsurgical pN1/pT2b/ stump (+)	WP+PF×4 vs WP+PAN	WP:45Gy WP+PAN	P:70/Day1 F:1000/Days1–4, q 3 Weeks	268	81 vs 71 (4 Years)	0.007

CT, chemotherapy; RT, radiotherapy; WP, whole pelvis; PAN, paraaortic lymph node; Adj, adjuvant; ATH, abdominal total hysterectomy; P, cisplatin; F, 5-FU; HU, hydroxyurea; Ra, radium therapy

RT combined with concurrent 5-FU, hyperfractionated RT alone, and hyperfractionated RT combined with concurrent 5-FU. There was a trend toward higher response rates and 5-year DFS in the CCRT arms compared with the RT arms, but the differences were not statistically significant. However, a subgroup analysis by disease stage found a higher 5-year DFS in the RT + 5-FU arm (n = 61) than in the standard RT arm (n = 45) for patients in stage IB2 to IIB (61% vs 45%; P = 0.05).

Thus, results from these early studies did not establish the efficacy of CCRT over RT alone with respect to either tumor response or survival.

Results of large randomized controlled studies of CCRT using CDDP-based regimens (1999)

In 1999, five large RCTs demonstrated the efficacy of concurrent CCRT using CDDP-based regimens (Table 3).

(1) In the GOG 85 trial (Whitney et al.[28]) patients with paraaortic lymph node (PAN)-negative stage IB to IVA disease were randomized to receive PF or HU, concurrently with RT. At a median follow-up of 7 years, DFS was significantly higher in patients who received PF (55% vs 43%; P = 0.0018).

(2) In the GOG 120 trial (Rose et al.[29]), patients with PAN-negative stage IIB to IVA disease were randomized to one of three treatment arms: RT with concurrent weekly CDDP, RT with concurrent PF plus HU, and RT with concurrent HU. The 3-year survival rate was significantly higher in the two arms using CDDP-based regimens, i.e., the weekly CDDP and PF + HU arms,

(66% and 67%, respectively) than in the HU arm (50%; P = 0.004 and P = 0.002, respectively).

(3) In the GOG 123 trial (Keys et al.[30]), RT combined with concurrent weekly CDDP followed by adjuvant hysterectomy was compared with RT alone followed by adjuvant hysterectomy in patients with PAN-negative stage IB2 disease. The 3-year survival rate was significantly higher in the CCRT arm (83% vs 74%; P = 0.008).

These three studies demonstrated the efficacy of CCRT in patients with PAN-negative disease.

(4) The Radiation Therapy Oncology Group (RTOG) 90-01 trial (Morris et al.[31]) compared CCRT, using PF, versus RT alone in patients with stage IB to IVA disease (stage IB/IIA with lymph node involvement or tumors 5cm or greater, and stage IIB-IVA). CCRT was associated with significantly higher 5-year OS (83% vs 58%; P = 0.004) and 5-year DFS (67% vs 40%; P < 0.001), as well as significantly lower distant and local recurrence rates (P < 0.001). However, efficacy of CCRT was not observed for patients with advanced disease; in a subset of patients with stage III/IVA disease, no statistically significant difference was found in 5-year survival rates (63% vs 57%).

Long-term follow-up of these patients revealed a significantly higher 8-year survival rate in patients who received CCRT (67% vs 41%; P < 0.001), while the incidence of serious late complications was similar in the two arms. Similar to the initial report, this long-term analysis also failed to demonstrate efficacy for stage III/IVA patients; a subgroup analysis by disease stage revealed that CCRT significantly

improved both OS and DFS in stage IB to IIB patients ($P <$ 0.0001), but in 116 stage III/IVA patients, there were only nonsignificant trends in favor of the CCRT arm with respect to PFS (59% vs 45%; $P = 0.05$) and OS (59% vs 45%; $P = 0.07$).[33]

(5) In the Southwestern Oncology Group (SWOG) 8797 trial (Peters et al.[32]), the efficacy of CCRT using PF was compared with RT alone in the postoperative adjuvant setting in stage IA2 to IIA patients who were found to have poor prognostic factors (lymph node involvement, parametrial involvement, and/or positive surgical margins of the vagina). The 4-year DFS was significantly higher in the CCRT arm (81% vs 71%; $P = 0.007$).

Thus, all of these five large studies demonstrated a significant survival benefit for patients treated with CCRT using a CDDP-based regimen, with a 28%–50% relative reduction in the risk of death (Fig. 1).[34] In response to these results, in 1992, the United States National Cancer Institute released a clinical alert stating that patients who require RT for treatment of cervical cancer should be treated with concurrent CT.[35]

Following these reports, results were reported from a large metaanalysis of all known 19 RCTs of CCRT conducted between 1981 and 2000, involving a total of 4580 cervical cancer patients.[36] In this metaanalysis (conducted using the methodology of the Cochrane Collaboration), CCRT significantly improved OS (HR, 0.71 [i.e., 29% reduction in the risk of death]; $P < 0.0001$; in 11 studies including 2865 patients), as well as PFS (HR, 0.61; $P < 0.0001$; in 13 studies including 3611 patients). The absolute benefits in PFS and OS were 16% (95% confidence interval [CI] 13–19) and 12% (95% CI, 8–16), respectively. The survival benefit was greater when CDDP was used (HR 0.70; $P < 0.0001$) than when it was not used (HR, 0.81; $P = 0.20$) and it was greater in patients with stage I/II disease than in those with more advanced disease ($P = 0.009$). Significant reductions in local recurrence (odds ratio, 0.61; 95% CI, 0.51–0.73; $P < 0.0001$) and distant recurrence (odds ratio, 0.57; 95% CI, 0.46–0.77; $P < 0.0001$) were also observed (12 studies including 3186 patients). Another metaanalysis[37] also demonstrated that CCRT using a CDDP-based regimen reduced the risk of death (HR, 0.74; 95% CI, 0.64–0.86).

These large RCTs and large metaanalyses provide strong evidence for the superiority of CCRT over RT alone, making this treatment method the new standard for patients with advanced cervical cancer. In Japan, CCRT is currently being incorporated into the treatment of these patients. The following section discusses several questions and concerns regarding CCRT for cervical cancer.

Questions and concerns

There are several questions about patient selection (disease stage) for CCRT and optimal CCRT treatment, such as the regimen, dose, schedule, and timing of the CT, as well as the dose, radiation field, and timing of the RT, because the

above-mentioned five RCTs[28–32] (Table 3) were conducted in different patient populations, using different CCRT protocols.

More specifically, these studies included both patients with a tumor less than 4 cm in diameter (stage IA2/IB1) and those with more advanced disease (all stages but stage IVB). Some studies used CDDP alone, while other studies used CDDP in combination with 5-FU and/or HU as the concurrent CT. The dose and schedule of CDDP also varied between studies; CDDP was given at 40–75 mg/m² every 4 weeks in some studies and at 40 mg/m² weekly in others. Thus, there seems to be no uniform consensus on the optimal CT regimen. For RT, the radiation field was restricted to the pelvis in some studies, while it was extended from the pelvis to the PANs in other studies. In addition, RT was administered at different timings (prior to hysterectomy or postoperatively).

Results of a study by the national cancer institute of canada (NCIC) (2002)

In 2002, the National Cancer Institute of Canada (NCIC) reported negative outcomes in patients who received CCRT.[38,39] The study compared CCRT, using weekly CDDP (40 mg/m²), versus RT alone in 259 patients in stage IB2 to IVA with tumor 5 cm or greater and lymph node involvement, but failed to demonstrate the superiority of CCRT over RT alone; the 5-year survival rate was 62% in the CCRT arm, compared with 58% in the RT-alone arm. The authors pointed out that, in the above-mentioned five RCTs,[28–32] "the benefit of CT might have been exaggerated because of suboptimal RT treatment with respect to radiation dose or duration." In fact, the survival rates in the RT-alone arms were much lower in these studies when compared with those in Japanese studies. On the other hand, the study conducted by the NCIC might have been limited by potentially inadequate staging; the study might have erroneously enrolled a substantial number of patients with PAN metastasis, i.e., stage IVB (M1) disease, because patients were staged by nonsurgical procedures, including computed tomography scans (the positive predictive value of computed tomography scans has been reported to be as low as 34%[40]). Nevertheless, a combined analysis of the above-mentioned five RCTs[28–32] and this NCIC study still demonstrated the efficacy of CCRT, with a 36% improvement in survival and a 12% reduction in local recurrence (Fig. 1).[34]

Adverse events

The incidence and severity of acute hematological and gastrointestinal toxicities were apparently higher when CCRT was used (Table 4).[36] CCRT significantly increased the incidence of grade III/IV leukopenia (odds ratio, 2.21), thrombocytopenia (odds ratio, 3.73) and gastrointestinal toxicity (odds ratio, 2.22). On the other hand, acute urogenital adverse events were significantly less frequent in the CCRT arm. These results are consistent with that obtained from a systematic review conducted by Kirwan et al.[41]

Fig. 1. Reduction in the risk (1-relative risk [RR]) of death in six clinical trials of chemoradiation in patients with cervical cancer. *GOG*, Gynecologic Oncology Group; *SWOG*, Southwest Oncology Group; *RTOG*, Radiation Therapy Oncology Group; *NCIC*, National Cancer Institute, of Canada; *5FU*, 5-fluorouracil; *H*, hydroxyurea; *CI*, confidence interval. From reference 34, with permission
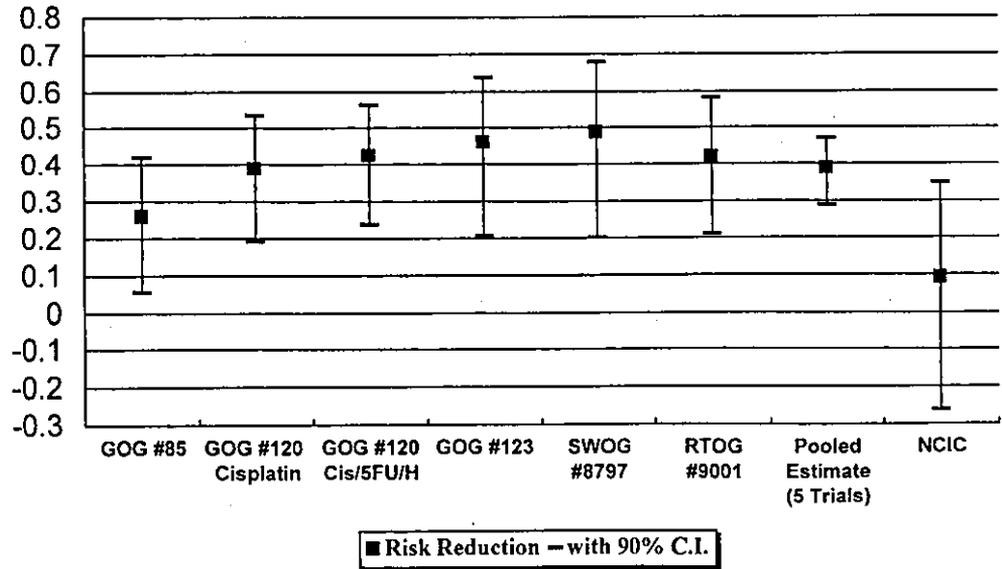

Table 4. Grade 3/4 acute toxicity in chemoradiotherapy

Toxicity	No. of trials	CCRT (%)	Control (%)	Odds ratio	95% CI	*P*-Value
Hematological						
Leukopenia	9	16.3	7.6	2.21	1.72–2.93	<0.0001
Platelets	8	1.5	0.2	3.73	1.53–9.10	0.004
Hemoglobin	6	5.6	3.8	1.49	0.98–2.27	0.06
Others	3	28.7	1.3	8.60	5.81–12.74	<0.0001
Non-hematological						
Gastrointestinal	6	9.55	4.3	2.22	1.58–3.11	<0.0001
Genitourinary	6	0.8	1.9	0.43	0.20–0.92	0.03
Neuropathy	3	0.5	0.4	1.11	0.19–6.56	0.90
Skin	4	1.8	1.6	1.09	0.50–2.39	0.80

CCRT, concurrent chemoradiotherapy; 95% CI, 95% confidence interval
Adapted from reference 36 with permission

Although long-term data are insufficient to assess the late complications associated with CCRT, published reports, including an update report of the RTOG 90-01 trial,[33] with a median follow-up of 6.6 years, found no significant difference in the incidence of late complications. Nevertheless, the long-term outcomes of patients treated with CCRT should be followed continuously because of a potential increase in the incidence or severity of late complications.

Thus, before CCRT is widely accepted as the standard treatment for cervical cancer, well-designed large RCTs need to be conducted to address the questions and concerns discussed in this section, especially the question arising from the negative results obtained in the NCIC study.

Combination of surgery and CCRT

Postoperative CCRT

In the above-mentioned SWOG 8797 trial,[32] involving 268 patients with stage IA2 to IIA disease who were found to have poor prognostic factors after surgery, the 4-year DFS

was significantly higher in patients who received RT combined with concurrent PF than in those who received RT alone as adjuvant therapy.

Preoperative CCRT

In the above-mentioned GOG 123 trial,[30] involving patients with stage IB2 disease without PAN involvement, the 3-year survival rate was significantly higher in patients who received CCRT than in those who received RT alone in the neoadjuvant setting (83% vs 74%; $P = 0.008$).

In another study, reported by Jurado et al.,[42] patients with stage IB2 to IVA disease were treated with CCRT, using the PF regimen, followed by hysterectomy plus pelvic lymph node adenectomy (PLA) with or without paraaortic lymph node adenectomy (PALA), or CCRT without surgery. While the response rate to CCRT was only 55%, the prognosis was favorable, with a 9-year survival of 85% when surgery was performed after CCRT. However, CCRT followed by surgery was associated with a higher incidence of serious adverse events; 3 (8%) and 5 (13%) patients,

respectively, experienced ureterovaginal fistula and hydronephrosis requiring ureteral stenting.

Mancuso et al.[43] reported the therapeutic outcomes of patients with stage IIB/IIIA disease who were treated with CCRT using the PF regimen, followed by radical hysterectomy. The response rate to CCRT was 100%; 64% and 36% of patients achieved CR and partial response (PR), respectively. The 2-year local control rate was high, at 91.7%. However, many patients experienced serious adverse events, including intraoperative bladder or urinary tract damage in four patients (16.7%), postoperative bilateral hydronephrosis requiring nephrostomy in two patients (8.2%), and postoperative renal failure leading to death in one patient (4.2%).

These results suggest that patients treated with CCRT followed by surgery may have a favorable prognosis, but are more likely to experience serious adverse events during or after surgery. Therefore, further investigation is required, with respect to patient selection criteria for surgery, operative procedure, and strategies for managing adverse events to maintain the quality of life (QOL) of patients.

Studies of CRT in Japan (Table 5[44–47])

In Japan, there are no reports of RCTs to evaluate CRT for cervical cancer. So far, only a limited number of small phase I/II studies have been reported.

All of these phase I/II studies employed platinum (CDDP or nedaplatin [CDGP]). In a study conducted by Kamiura and Saji,[47] patients with stage IB disease, which is more frequently diagnosed, and more advanced disease (to stage IVB) received CCRT following primary or postoperative adjuvant RT. In this study, CCRT demonstrated no efficacy in any subsets of patients when compared with historical controls; for stage I/II patients who received CCRT following postoperative adjuvant RT, there was only a nonsignificant trend toward an improved 3-year cumulative survival rate. For stage III/IV patients who received CCRT following primary RT, there was no improvement in survival rate, and the sites of metastasis or recurrence were similar to those observed in historical control arms.

Toita et al.[44] also reported that they found no superiority of CCRT over the historical controls they used.

Fuwa et al. (Department of Radiation Therapy, Aichi Cancer Center Hospital) conducted a phase I/II study of alternating CRT using high-dose CDGP plus 5-FU in patients with advanced (stage III to IVB) cervical cancer or recurrent cervical cancer pretreated with RT (unpublished data; article in preparation). The treatment protocol was based on their results[48] from a phase I study mainly in patients with head and neck cancer. The recommended dose of CDGP in this regimen for newly diagnosed patients was determined to be as high as 140 mg/m^2. An objective response occurred in all 19 patients (CR in 16 and PR in 3 patients). At a median follow-up of 23 months, 4 of the 19 patients (2 of 7 in stage IIIB and 2 of 6 in stage IVB) had developed recurrence, while the other 15 patients were alive without evidence of disease. The 2-year DFS was quite high, at 78%, in these 19 patients with bulky tumor of 5 cm or greater (stage IIB or more advanced stage), for which even local control is generally difficult. These results suggest that this therapy is promising to improve the prognosis of cervical cancer, and phase III studies are warranted.

Future issues and perspectives

CCRT seems to be effective for certain patient populations when used with certain treatment protocols. However, as mentioned above, there are several issues to be addressed.

Defining the patient population (disease stage) that will benefit from CCRT

In Japan, no detailed data restricted to patients with stage IB1 squamous cell carcinoma are available regarding survival outcomes after each therapeutic approach, but, for the entire group of patients with stage I disease, a 5-year survival rate of 80.4% may be achieved by the current standard treatment, consisting of surgery with or without adjuvant RT.[1] Because there are no CCRT regimens that resulted in

Table 5. Chemoradiotherapy in cervical cancer (Japan)

Author	Stage	Design	RT	CT (mg/m^2)	No. of patients	Result	Remarks
Toita,[44] 2000	IIB-IVA	Phase II	WP:50Gy+ HDR-RALS PAN:45Gy	CDDP:20, Days1–5, q 3 Weeks	22	2-Year survival rate: 57%	Distant metastasis-free rate, 72%
Horie,[45] 2002	IB1-IIIB and postsurgical	Phase II	WP:50Gy+α	CDDP:30–50 mg/m^2 or CDGP:100 mg/m^2, Day5+ 5-FU:500 mg/m^2,days 5–8, q 4 Weeks	13	RR:100% (9/9)	
Tanaka,[46] 2003	Advanced cancer	Phase I	WP:50Gy+ brachtherapy	Low-dose consecutive CDDP Starting dose: 6		Ongoing	
Kamiura,[47] 2004	IB-IVB and postsurgical	Phase II	WP:45Gy+ HDR-RALS PAN:45Gy	CBDCA:AUC:4 or CDGP:70, q 3 Weeks	64	Survival of historical controls (3 Years)	NS

CT, chemotherapy; RT, radiotherapy; WP, whole pelvis; PAN, paraaortic lymph node; HDR, high dose rate; RR, response rate; AUC, area under the concentration-time curve; RALS, remotely controlled affer-loading system