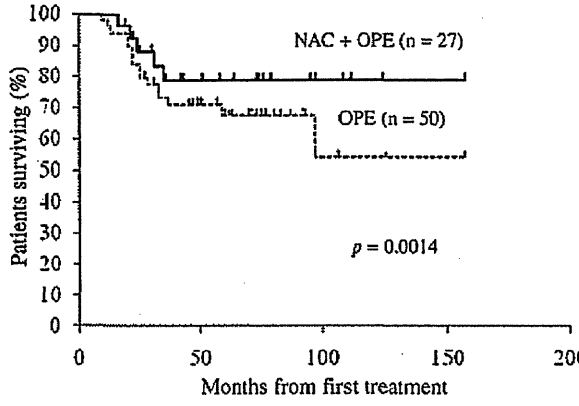
Fig. 1A



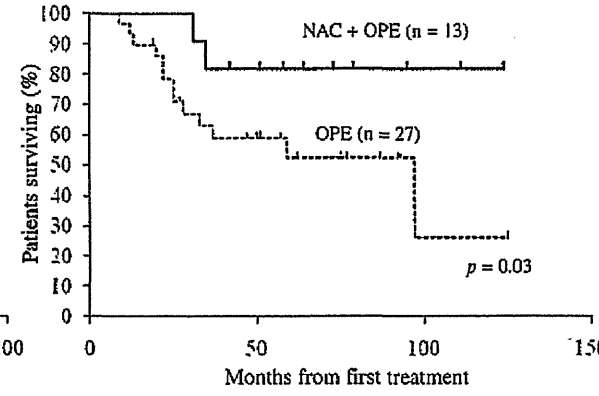


Fig. 1B

Figure 1. — 1A: overall survival in all patients who underwent neoadjuvant chemotherapy followed by radical hysterectomoy (NAC) or radical hysterectomy alone (RH). 1B: overall survival in patients with mucinous adenocarcinoma who underwent neoadjuvant chemotherapy followed by radical hysterectomoy (NAC) or radical hysterectomy alone (RH).

in uterine cervical carcinoma [18]. Considering these reports together with the present results, chemoradiotherapy or radiotherapy after NAC and surgery may contribute to unfavorable outcome of the patients with uterine cervical adenocarcinoma compared to chemotherapy after NAC and surgery, although further investigation is necessary to confirm the appropriate therapeutic modality follwing NAC and surgery.

The recent reports demonstrated that taxanes were used effectively in NAC for uterine cervical adenocarcinoma [19, 20]. Most of the institutions joining TGCU had adopted cisplatin-based regimens in the 1990s, and switched to the regimens combining taxanes and platinum derivatives after 2000. Despite the diverse NAC regimens and the small sample size, the authors believe that the present results have provided constructive ideas for the development of new therapeutic strategy for N-SCC of the uterine cervix. An effective chemotherapeutic regimen for N-SCC of the uterine cervix should be urgently integrated in a phase II study and then a RCT that compares a new single NAC and radical surgery with radical surgery alone, is warranted to confirm the present results.

Acknowledgements

The authors thank the medical staff in the institutions joining Tohoku Gynecologic Cancer Unit for clinical review of this study.

References

[1] Whitney C.W., Sause W., Bundy B.N., Malfetano J.H., Hannigan E.V., Fowler W.C. Jr. *et al.*: "Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in Stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study". *J. Clin. Oncol.*, 1999, *17*, 1339.

[2] Morris M., Eifel P.J., Lu J., Grigsby P.W., Levenback C., Stevens R.E. *et al.*: "Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer". *N. Engl. J. Med.*, 1999, *340*, 1137.

[3] Rose P.G., Bundy B.N., Watkins E.B., Thigpen J.T., Deppe G., Maiman M.A. *et al.*: "Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer". *N. Engl. J. Med.*, 1999, *340*, 1144.

[4] Keys H.M., Bundy B.N., Stehman F.B., Muderspach L.I., Chafe W.E., Suggs C.L. 3rd *et al.*: "Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky Stage 1B cervical carcinoma". *N. Engl. J. Med.*, 1999, *340*, 1154.

[5] Peters W.A. 3rd, Liu P.Y., Barrett R.J. 2nd, Stock R.J., Monk B.J., Berek J.S. *et al.*: "Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix". *J. Clin. Oncol.*, 2000, *18*, 1606.

[6] Thomas G.M.: "Improved treatment for cervical cancer-concurrent chemotherapy and radiotherapy". *N. Engl. J. Med.*, 1999, *340*, 1198.

[7] Green J.A., Kirwan J.M., Tierney J.F., Symonds P., Fresco L., Collingwood M. *et al.*: "Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis". *Lancet*, 2001, *358*, 781.

[8] Benedetti-Panici P., Greggi S., Colombo A., Amoroso M., Smaniotto D., Giannarelli D. *et al.*: "Neoadjuvant chemotherapy and radical surgery versus exclusive radiotherapy in locally advanced squamous cell cervical cancer: results from the Italian multicenter randomized study". *J. Clin. Oncol.*, 2002, *20*, 179.

[9] Nagao S., Fujiwara K., Oda T., Ishikawa H., Koike H., Tanaka H. *et al.*: "Combination chemotherapy of docetaxel and carboplatin in advanced or recurrent cervix cancer. A pilot study". *Gynecol. Oncol.*, 2005, *96*, 805.

[10] Shoji T., Takatori E., Hatayama S., Omi H., Kagabu M., Honda T. *et al.*: "Phase II Study of Tri-weekly cisplatin and irinotecan as neoadjuvant chemotherapy for locally advanced cervical cancer". *Oncol. Lett.*, 2010, *1*, 515.

[11] Sardi J.E., Giaroli A., Sananes C., Ferreira M., Soderini A., Bermudez A. *et al.*: "Long-term follow-up of the first randomized trial using neoadjuvant chemotherapy in Stage Ib squamous carcinoma of the cervix: The final results". *Gynecol. Oncol.*, 1997, *67*, 61.

[12] Serur E., Mathews R.P., Gates J., Levine P., Maiman M., Remy J.C.: "Neoadjuvant chemotherapy in stage IB2 squamous cell carcinoma of the cervix". *Gynecol. Oncol.*, 1997, *65*, 348.

[13] Shingleton H.M., Gore H., Bradley D.H., Soong H.J.: "Adenocarcinoma of the cervix : I. Clinical evaluation and pathologic features". *Am. J. Obstet. Gynecol.*, 1981, *139*, 799.
[14] Fu Y.S., Reagan J.W., Hsui J.G., Storaasli J.P., Wemtz W.B.: "Adenocarcinoma and mixed carcinoma of the cervix: A clinicopathologic study". *Cancer*, 1982, *49*, 2560.
[15] Berek J.S., Hacker N.F., Fu Y., Sokale J.R., Leucher R.C., Lagasse L.D.: "Adenocarcinoma of the uterine cervix: histlogic variables associated with lymph node metastasis and survival". *Obstet. Gynecol.*, 1985, *65*, 46.
[16] Moberg P.J., Einhorn N., Silfverswärd C., Söderberg G.: "Adenocarcinoma of the cervix". *Cancer*, 1986, *57*, 407.
[17] Tattersall M.H., Lorvidhaya V., Vootiprux V., Cheirsilpa A., Wong F., Azhar T. *et al.*: "Randomized trial of epirubicin and cisplatin chemotherapy followed by pelvic radiation in locally advanced cervical cancer. Cervical Cancer Study Group of the Asian Oceanian Clinical Oncology Association". *J. Clin. Oncol.*, 1995, *13*, 444.
[18] Neoadjuvant Chemotherapy for Locally Advanced Cervical Cancer Meta-analysis Collaboration: "Neoadjuvant chemotherapy for locally advanced cervical cancer: a systematic review and meta-analysis of individual patient deta from 21 randomized trials". *Eur. J. Cancer*, 2003, *39*, 2470.
[19] Oguri H., Maeda N., Fukaya T.: "Cervical adenocarcinoma treated with docetaxel and carboplatin". *Int. J. Gynaecol. Obstet.*, 2003, *83*, 209.
[20] Huang X., Lan C., Huang H., Zhang Y., Huang H., Cao X. *et al.*: "Neoadjuvant docetaxel combined with cisplatin and followed by radical surgery for the treatment of locally advanced (Stage IB2 - IIB) cervical cancer: preliminary results of a single-institution experience". *Expert Opin. Pharmacother.*, 2011, *12*, 165.

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Tohoku J. Exp. Med., 2012, 228, 365-370

Hysteroscopic Inspection and Total Curettage Are Insufficient for Discriminating Endometrial Cancer from Atypical Endometrial Hyperplasia

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Endometrial cancer (EC) is the most prevalent gynecologic malignancy in Japan. Atypical endometrial hyperplasia (AEH) is viewed as the premalignant lesion of EC, however it is often difficult to distinguish EC from AEH. The rate of concurrent EC in women diagnosed preoperatively with AEH based on endometrial biopsy was reported as 17-52%. Although hysteroscopic inspection and total curettage are considered as useful methods to make diagnosis of endometrial lesions, there is no report using this combined method to discriminate EC from AEH. The purpose of this study was to examine whether hysteroscopic inspection and total curettage improve the prevalence of EC among women diagnosed preoperatively with AEH. We reviewed 22 patients who underwent hysteroscopic inspection and total curettage and were diagnosed with AEH before undergoing hysterectomy between November 2001 and May 2011. The diagnosis made with the hysterectomy specimens revealed AEH in 10 patients (45.5%), endometrial hyperplasia without atypia in 3 (13.6%), and endometrioid adenocarcinoma, the most common type of EC, in 9 (40.9%). Endometrioid adenocarcinoma included 7 patients without myometrial invasion (31.8%) and 2 patients with superficial myometrial invasion (9.1%). There was no hysteroscopic finding that was specific for EC or AEH. In conclusion, about 41% of women who underwent hysterectomy under a diagnosis of AEH were found to have coexisting adenocarcinoma, although the prevalence of EC among those women was similar to that in earlier reports with endometrial biopsy. Accordingly, we must be careful in planning the therapeutic strategy for women with a preoperative diagnosis of AEH.

Keywords: Atypical endometrial hyperplasia; endometrial cancer; hysteroscopy; myometrial invasion; total curettage
Tohoku J. Exp. Med., 2012 Dec, **228** (4), 365-370.

Endometrial cancer (EC) is the most common gynecologic malignancy in Europe and the United States. EC has also increased in Japan in the last 20 years, and in 2009 moved ahead of cervical cancer as the most prevalent malignant gynecologic disease in Japan (Sakuragi et al. 2010). Endometrioid adenocarcinoma is the most common pathologic type of EC, and adenomatous hyperplasia was shown to be a premalignant lesion of endometrioid adenocarcinoma 50 years ago (Gusberg and Kaplan 1963). Currently, endometrial hyperplasia, atypical endometrial hyperplasia (AEH) and well-differentiated endometrioid adenocarcinoma are viewed as a continuous spectrum of the disease. Kurman et al. (1985) classified hyperplasia as simple hyperplasia without atypia, complex hyperplasia without atypia, simple atypical hyperplasia, and complex atypical hyperplasia with cellular atypia and architectural atypia. They found that the rates of progression to EC from simple hyperplasia without atypia, complex hyperplasia without atypia, simple atypical hyperplasia and complex atypical hyperplasia were 1%, 3%, 8% and 29%, respectively (Kurman et al. 1985). The World Health Organization (WHO) and the International Society of Gynecologic Pathologists (ISGP) now use this classification.

In patients diagnosed as AEH with endometrial biopsy, the reported rate of concurrent endometrial adenocarcinoma in hysterectomy specimens is 17-52% (Kurman and Norris 1982; Dunton et al. 1996). The prevalence of EC with

Received June 18, 2012; accepted October 22, 2012. Published online November 16, 2012; doi: 10.1620/tjem.228.365.
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myometrial invasion was also reported as 8-39% (Kurman and Norris 1982; Merisio et al. 2005). Because of the high rate of concomitant cancer, even if endometrial atypical hyperplasia is diagnosed with endometrial biopsy, complete endometrial curettage is recommended in the Japan Society of Gynecologic Oncology guidelines for treatment of uterine body neoplasms (Nagase et al. 2010). However, only a few studies examined endometrial adenocarcinoma in hysterectomy specimens after diagnosis of AEH with total curettage (Shutter and Wright 2005; Merisio et al. 2005; Trimble et al. 2006), and there is no report using hysteroscopic inspection and total curettage preoperatively. The purpose of this study was to examine whether hysteroscopic inspection and total curettage are sufficient for diagnosing AEH. In this study, we reviewed the pathological diagnosis of hysterectomy specimens in women diagnosed as AEH with hysteroscopic inspection and total curettage. The primary endpoint was the prevalence of endometrial adenocarcinoma. Secondary endpoints were the rate of myometrial invasion and the grade of endometrioid adenocarcinoma.

Patients and Methods

The subjects were 22 patients who were diagnosed with AEH based on hysteroscopic inspection and total curettage, and then underwent total hysterectomy between November 2001 and May 2011 in the Department of Gynecology, Tohoku University Hospital. The indications for hysteroscopic inspection and total curettage in our institute were women diagnosed with AEH by endometrial biopsy; referred with a diagnosis of AEH; clinically suspected to have AEH or endometrial cancer by endometrial cytology or imaging studies, although these diagnoses were not made with endometrial biopsy; or under treatment with medroxyprogesterone acetate (MPA) therapy for AEH or early stage EC. Patients treated with MPA to preserve fertility were excluded from the study.

Hysteroscopic inspection and total curettage were performed in three steps under intravenous anesthesia as a day case admission: 1) insertion of a flexible scope into the uterine cavity for filling with isotonic sodium chloride as a distension medium, and inspection for the presence of an elevated lesion, atypical vessel or necrotic tissue; 2) thorough curettage of the uterine cavity with particular attention to endometrial lesions; and 3) reinsertion of a hysteroscope to ensure that all endometrial lesions had been removed. Clinical information and hysteroscopic findings were obtained from medical records. The primary doctor made a pathological diagnosis and two other doctors reviewed this decision and established the final diagnosis. A pathological diagnosis of non-atypical hyperplasia in the hysterectomy specimen was regarded as AEH.

Results

Of the 22 patients, the diagnoses made with the hysterectomy specimens were AEH in ten patients (45.5%), endometrial hyperplasia without atypia in three patients (13.6%), and endometrioid adenocarcinoma in nine patients (40.9%). The AEH patients included two patients with simple atypical hyperplasia and eight patients with complex atypical hyperplasia. The three patients diagnosed with endometrial hyperplasia without atypia showed complex hyperplasia without atypia. Endometrioid adenocarcinoma included seven grade 1 (G1) patients without myometrial invasion, one G1 patient with superficial myometrial invasion, and one grade 2 (G2) patient with superficial myometrial invasion, giving a total of seven patients (31.8%) without myometrial invasion and two patients (9.1%) with superficial myometrial invasion (Table 1). Total hysterectomy with bilateral salpingo-oophorectomy was performed in 21 patients, and total hysterectomy with preservation of the ovaries was performed in one patient diagnosed with AEH based on the hysterectomy specimen. No patient has shown recurrence up to May 2012.

Comparison of the patients with endometrioid adenocarcinoma (EC group, n = 9) and all other patients (AEH group, n = 13) showed no significant differences in age, menstrual status, parity, body mass index (BMI), symptoms, thickness of the endometrium measured by trans-vaginal ultrasonography, and time from diagnosis to hysterectomy (Table 2).

Hysteroscopic findings of an elevated lesion, atypical vessel or necrosis also did not differ significantly between the two groups (Table 3). MRI information was available

Table 1. Diagnosis based on the hysterectomy specimen.

Diagnosis from hysterectomy	No. of patients	(%)
Non-atypical endometrial hyperplasia	3	13.6
Simple hyperplasia	0	
Complex hyperplasia	3	
Atypical endometrial hyperplasia (AEH)	10	45.5
Simple atypical hyperplasia	2	
Complex atypical hyperplasia	8	
Endometrial carcinoma (EC)	9	40.9
Endometrioid adenocarcinoma 1a Grade1	7	
Endometrioid adenocarcinoma 1b Grade1	1	
Endometrioid adenocarcinoma 1b Grade2	1	
Total	22	

Table 2. Comparison of clinical parameters between patients in the EC and AEH groups.

Clinical parameter	EC $n = 9$	AEH $n = 13$	P
Age	53.4 (± 9.1)	53.4 (± 8.3)	0.57
Post-menopause	3 (33%)	6 (46%)	0.67
Parity	1.7 (± 1.0)	1.3 (± 1.2)	0.51
BMI	22.8 (± 3.7)	23.4 (± 4.5)	0.54
Abnormal genital bleeding	5 (56%)	10 (77%)	0.38
Endometrial thickness (mm)	20.9 (± 12.6)	14.4 (± 8.5)	0.25
Time from diagnosis to hysterectomy (days)	58 (± 17)	80 (± 122)	0.38

Values are shown as a mean (± S.D.) or the number of patients (%). EC, endometrial cancer; AEH, atypical endometrial hyperplasia; BMI, body mass index.

Table 3. Comparison of hysteroscopic findings between patients in the EC and AEH groups.

Hysteroscopic findings[a]	EC $n = 9$	AEH $n = 13$
Elevated lesion	6 (66%)	9 (69%)
Atypical vessel	2 (22%)	2 (15%)
Necrosis	0 (0%)	0 (0%)
No finding	2 (22%)	3 (23%)

Values are shown as the number of patients (%).
[a]Multiple findings were possible; therefore the totals are greater than 100%.
EC, endometrial cancer; AEH, atypical endometrial hyperplasia.

Table 4. Comparison of MRI findings between patients in the EC and AEH groups.

MRI findings[a]	EC group $n = 8$	AEH group $n = 11$
Endometrial abnormal signals[b]	4 (50%)	5 (45%)
Laceration of junctional zone	2 (25%)	2 (18%)
No findings	4 (50%)	6 (55%)

Values are shown as the number of patients (%). EC, endometrial cancer; AEH, atypical endometrial hyperplasia; MRI, magnetic resonance imaging.
[a] Multiple findings were possible; therefore the totals are greater than 100%.
[b] Heterogenous intensity or intermediate to low intensity lesion.

for eight patients in the EC group and 11 patients in the AEH group (Table 4). The exceptions were two patients in the AEH group and one patient with superficial myometrial invasion in the EC group. Abnormal endometrial signals (heterogenous intensity or intermediate to low intensity) were observed in 50% of EC patients and 45% of AEH patients. In the grade 1 patient with superficial myometrial invasion, the junctional zone was intact. The association between laceration of the junctional zone and myometrial invasion was unclear, and two EC patients and three AEH patients were incorrectly judged to have laceration of the junctional zone. MRI findings were similar between the two groups. We also analyzed whether hysteroscopic findings were concordant with MRI findings in patients who underwent MRI (n = 19). Endometrial elevated lesions were detected in eight patients (42%) by both hysteroscopy and MRI, in four patients (21%) by hysteroscopic inspection, and in one patient (5%) by MRI, whereas they were not detected by either method in 6 patients (32%) (data not shown).

Discussion

In this retrospective study, 41% of women who underwent hysterectomy under a diagnosis of AEH were found to have coexisting endometrial adenocarcinoma. These results are similar to those in previous reports (Table 5) (Kurman and Norris 1982; Janicek and Rosenshein 1994; Lambert et al. 1994; Hunter et al. 1994; Liapis et al. 1994; Widra et al. 1995; Dunton et al. 1996; Xie et al. 2002; Agostini et al. 2002; Kimura et al. 2003; Bilgin et al. 2004; Shutter and Wright 2005; Merisio et al. 2005; Garuti et al. 2006; Trimble et al. 2006; Dordević et al. 2007). Sampling errors

Table 5. Prevalence of concurrent EC in women with a preoperative diagnosis of AEH.

Author	Number of patients	Endometrium sampling method (number of cases)	Prevalence of concurrent EC (%)	Prevalence of myometrial invasion (%)
Kurman, 1982	89	Curettage (89)	17	8
Janicek, 1994	44	Biopsy (25)/D and C (19)	43 (40/47)[a]	39
Lambert, 1994	29	Curettage (29)	21	Not recorded
Hunter, 1994	54	Biopsy/Curettage	35	26
Liapis, 1994	73	Curettage (73)	36	Not recorded
Widra, 1995	24	Biopsy/Curettage	50	38
Dunton, 1996	23	Biopsy/D and C	52	26
Xie, 2002	86	Curettage (86)	38	Not recorded
Agostini, 2002	17	Hysteroscopy resection (17)	6	0
Kimura, 2003	33	Biopsy (33)	27	9
Bilgin, 2004	46	Biopsy (8)/Curettage (38)	24 (25/24)[a]	20
Shutter, 2005	60	Biopsy (30)/D and C (30)	48 (57/40)[a]	35
Merisio, 2005	70	Biopsy (31)/D and C (39)	43 (45/41)[a]	39
Garuti, 2006	25	Hysteroscopy resection (25)	44	32
Trimble, 2006	289	Biopsy (181)/D and C (108)	43 (52/26)[a]	13
Dordevic, 2007	72	Curettage (72)	28	Not recorded
Current study	22	Hysteroscopic inspection and D and C (22)	41	9
Total	1,056		35	23

[a] Prevalence of EC by biopsy / prevalence of EC by D and C. EC, endometrial cancer; AEH, atypical endometrial hyperplasia; D and C, dilatation and curettage.

may account for the failure of diagnosis of EC. In one EC patient, a submucosal myoma might have prevented adequate sampling. In six EC patients, elevated lesions were found in hysteroscopy, and we checked whether these lesions were removed after total curettage; however, focal malignant lesions might not have been removed. Epstein et al. (2001) reported that in 87% of women with an endometrium > 5 mm and focal lesions in the uterine cavity, all or a part of the lesion remained in situ after dilatation and curettage. Thus, complete removal of an endometrial lesion is difficult even with total curettage. In the other two EC patients, hysteroscopy showed only atrophic endometrium, and it was unclear whether all of the lesions had been removed.

For an occult lesion, diagnostic procedures in addition to conventional hysteroscopy are required. Narrow band imaging (NBI) is a new endoscopic technique for better visualization of mucosal microstructures and capillary structures, and may be promising for diagnosis of gastrointestinal lesions. Surico et al. (2009) first reported that NBI could be a useful methodology for early detection of endometrial lesions. Kisu et al. (2011) found that the sensitivity of diagnosis of AEH or EC was significantly higher using white light + NBI compared to white light only, without a decline in the specificity of diagnosis. In a large-scale multicenter study, Tinelli et al. (2011) found that NBI significantly improved the sensitivity (60% vs. 20%, $P < 0.005$) and positive predictive value (67% vs. 25%, $P < 0.001$) compared with white light only for diagnosis of high-risk hyperplasia, with no differences in specificity, negative predictive value, and accuracy. These reports indicate that NBI may be a useful procedure to complement a hysteroscopic examination, and NBI may become established in standard clinical practice in the near future.

In our institute, three doctors participate in pathological diagnosis for each patient to avoid misdiagnosis. Therefore, we believe that the diagnosis made is valid. In 2006, the GOG study found EC in hysterectomy specimens in 14 of 74 patients (18.9%) with a study panel consensus diagnosis of "less than AEH", and in 54 of 84 patients (64.3%) with a consensus diagnosis of carcinoma (Trimble et al. 2006). However, the prevalence of EC among women diagnosed with AEH by study panel review was also relatively high (39.1%), which suggests that improvement of diagnostic accuracy for EC may be difficult based only on pathological diagnosis.

During a hysteroscopic examination, cancer cell dissemination into the peritoneal cavity may occur due to the pressure of the medium used for distention of the uterine cavity. In the present study, information on peritoneal cytology was available for 11 patients in the AEH group and all patients in the EC group. Peritoneal cytology was negative in all patients in the AEH group, and there was only one patient that was suspicious and no patients that were positive in the EC group. We used isotonic sodium chloride to inflate the uterine cavity, without use of a device to apply pressure. Chang et al. (2011) conducted a meta-analysis of the effect of hysteroscopy on peritoneal dissemi-

nation of endometrial cancer cells. The risk was significantly associated with the use of a liquid medium for uterine cavity distention, but not with early-stage disease, although hysteroscopic examination in patients with endometrial cancer may increase the risk of dissemination of malignant cells into the peritoneal cavity. In addition, there was no evidence to support an association between preoperative hysteroscopic examination and a worse prognosis. Thus, Chang et al. (2011) concluded there is no reason to avoid diagnostic hysteroscopy before surgery in patients with endometrial cancer, especially in the early stage.

An endometrial lesion was not detected with MRI in more than half of our patients in both the EC and AEH groups. Thus, the utility of MRI for detection of myometrial invasion was unclear in this study, but T2WI has been shown to be useful for evaluation of myometrial invasion (Messiou et al. 2006). Dynamic imaging is useful for detection of myometrial invasion when the junctional zone is unclear because of age, myoma uteri, adenomyosis uteri, and deformity of the uterus (Messiou et al. 2006). Thus, MRI is useful for detection of deep myometrial invasion, but it is difficult to distinguish early stage EC from AEH in an endometrial lesion detected by MRI. To our knowledge, differentiation of these lesions has not been achieved, although the apparent diffusion coefficient (ADC) is effective for distinguishing EC from normal endometrium or a benign endometrial lesion (Tamai et al. 2007; Takeuchi et al. 2009). Use of this parameter for distinguishing early EC from AEH requires further examination.

A summary of previous reports of the prevalence of endometrial cancer among women with a preoperative diagnosis of AEH is shown in Table 5. Total curettage is generally viewed as superior to biopsy, but the available data do not clearly show the superiority of either technique, partly because several reports do not describe the method of preoperative diagnosis with clarity: for example, curetting may indicate biopsy or total curettage. In the 2006 large-scale prospective GOG study, the prevalences of endometrial adenocarcinoma among women diagnosed by dilatation and curettage (D and C) and by biopsy were 26% and 52%, respectively (Trimble et al. 2006). These results show a surprisingly high prevalence of EC among women with a preoperative diagnosis of AEH, but they are supported by reports of similar prevalences of EC after diagnosis of AEH by D and C (Janicek and Rosenshein 1994; Dunton et al. 1996; Shutter and Wright 2005; Merisio et al. 2005; Trimble et al. 2006) (Table 5). In this study, we also found a similar prevalence of endometrial adenocarcinoma, even after diagnosis of AEH with hysteroscopic inspection and total curettage. Thus, even with the combined use of these methods, it is difficult to detect localized EC. This is an important consideration in planning a therapeutic strategy for women with a preoperative diagnosis of AEH.

In the current study, the percentage of patients with myometrial invasion was lower than that in other studies (Table 5). To the best of our knowledge, the rates of myometrial invasion in women diagnosed with endometrial biopsy or total curettage have not been compared. A tumor with myometrial invasion is likely to expand on the endometrial surface and becomes easier to be detected with hysteroscopy and biopsy. Therefore, hysteroscopic inspection and total curettage might improve the accuracy of diagnosis of advanced endometrial adenocarcinoma, especially in patients with myometrial invasion. This hypothesis requires validation through further accumulation of patients.

Conflict of Interest

No author has any conflict of interest.

References

Agostini, A., Cravello, L., Shojai, R., Schaeffer, V., Bretelle, F., Roger, V. & Blanc, B. (2002) Risk of finding an endometrial cancer when atypical hyperplasia was incidentally diagnosed on hysteroscopic resection products. *Eur. J. Obstet. Gynecol. Reprod. Biol.*, **103**, 58-59.

Bilgin, T., Ozuysal, S., Ozan, H. & Atakan, T. (2004) Coexisting endometrial cancer in patients with a preoperative diagnosis of atypical endometrial hyperplasia. *J. Obstet. Gynaecol. Res.*, **30**, 205-209.

Chang, Y.N., Zhang, Y., Wang, Y.J., Wang, L.P. & Duan, H. (2011) Effect of hysteroscopy on the peritoneal dissemination of endometrial cancer cells: a meta-analysis. *Fertil. Steril.*, **96**, 957-961.

Dordević, B., Stanojević, Z., Zivković, V., Lalosević, D., Gligorijević, J. & Krstić, M. (2007) Preoperative and postoperative histopathological findings in patients with endometrial hyperplasia. *Med. Pregl.*, **60**, 372-376.

Dunton, C.J., Baak, J.P., Palazzo, J.P., van Diest, P.J., McHugh, M. & Widra, E.A. (1996) Use of computerized morphometric analyses of endometrial hyperplasias in the prediction of coexistent cancer. *Am. J. Obstet. Gynecol.*, **174**, 1518-1521.

Epstein, E., Ramirez, A., Skoog, L. & Valentin, L. (2001) Dilatation and curettage fails to detect most focal lesions in the uterine cavity in women with postmenopausal bleeding. *Acta Obstet. Gynecol. Scand.*, **80**, 1131-1136.

Garuti, G., Mirra, M. & Luerti, M. (2006) Hysteroscopic view in atypical endometrial hyperplasias: a correlation with pathologic findings on hysterectomy specimens. *J. Minim. Invasive Gynecol.*, **13**, 325-330.

Gusberg, S.B. & Kaplan, A.L. (1963) Precursors of corpus cancer. IV. adenomatous hyperplasia as stage of carcinoma of the endometrium. *Am. J. Obstet. Gynecol.*, **87**, 662-678.

Hunter, J.E., Tritz, D.E., Howell, M.G., DePriest, P.D., Gallion, H.H., Andrews, S.J., Buckley, S.B., Kryscio, R.J. & van Nagell, J.R. Jr. (1994) The prognostic and therapeutic implications of cytologic atypia in patients with endometrial hyperplasia. *Gynecol. Oncol.*, **55**, 66-71.

Janicek, M.F. & Rosenshein, N.B. (1994) Invasive endometrial cancer in uteri resected for atypical endometrial hyperplasia. *Gynecol. Oncol.*, **52**, 373-378.

Kimura, T., Kamiura, S., Komoto, T., Seino, H., Tenma, K., Ohta, Y., Yamamoto, T. & Saji, F. (2003) Clinical over- and underestimation in patients who underwent hysterectomy for atypical endometrial hyperplasia diagnosed by endometrial biopsy: the predictive value of clinical parameters and diagnostic imaging. *Eur. J. Obstet. Gynecol. Reprod. Biol.*, **108**, 213-216.

Kisu, I., Banno, K., Kobayashi, Y., Ono, A., Masuda, K., Ueki, A., Nomura, H., Hirasawa, A., Abe, T., Kouyama, K., Susumu, N. & Aoki, D. (2011) Narrow band imaging hysteroscopy: a comparative study using randomized video images. *Int. J.*

Oncol., **39**, 1057-1062.
Kurman, R.J., Kaminski, P.F. & Norris, H.J. (1985) The behavior of endometrial hyperplasia. A long-term study of "untreated" hyperplasia in 170 patients. *Cancer*, **56**, 403-412.
Kurman, R.J. & Norris, H.J. (1982) Evaluation of criteria for distinguishing atypical endometrial hyperplasia from well-differentiated carcinoma. *Cancer*, **49**, 2547-2559.
Lambert, B., Muteganya, D., Lepage, Y. & Boivin, Y. (1994) Complex hyperplasia of the endometrium. Predictive value of curettage vs. hysterectomy specimens. *J. Reprod. Med.*, **39**, 639-642.
Liapis, A., Pafitis, A., Hassiakos, D., Chirakis, M. & Zourlas, P.A. (1994) Diagnostic histologic criteria of atypical adenomatous hyperplasia and well differentiated adenocarcinoma of the endometrium. *Eur. J. Gynaecol. Oncol.*, **15**, 464-468.
Merisio, C., Berretta, R., De Ioris, A., Pultrone, D.C., Rolla, M., Giordano, G., Tateo, S. & Melpignano, M. (2005) Endometrial cancer in patients with preoperative diagnosis of atypical endometrial hyperplasia. *Eur. J. Obstet. Gynecol. Reprod. Biol.*, **122**, 107-111.
Messiou, C., Spencer, J.A. & Swift, S.E. (2006) MR staging of endometrial carcinoma. *Clin. Radiol.*, **61**, 822-832.
Nagase, S., Katabuchi, H., Hiura, M., Sakuragi, N., Aoki, Y., Kigawa, J., Saito, T., Hachisuga, T., Ito, K., Uno, T., Katsumata, N., Komiyama, S., Susumu, N., Emoto, M., Kobayashi, H., Metoki, H., Konishi, I., Ochiai, K., Mikami, M., Sugiyama, T., Mukai, M., Sagae, S., Hoshiai, H., Aoki, D., Ohmichi, M., Yoshikawa, H., Iwasaka, T., Udagawa, Y., Yaegashi, N. & Japan Society of Gynecologic Oncology. (2010) Evidence-based guidelines for treatment of uterine body neoplasm in Japan: Japan Society of Gynecologic Oncology (JSGO) 2009 edition. *Int. J. Clin. Oncol.*, **15**, 531-542.
Sakuragi, N. (2010) Gynecologic oncology committee report. *Acta Obst. Gynaec. Jpn.*, **62**, 827-910 (in Japanese).
Shutter, J. & Wright, T.C. Jr. (2005) Prevalence of underlying adenocarcinoma in women with atypical endometrial hyperplasia. *Int. J. Gynecol. Pathol.*, **24**, 313-318.
Surico, D., Vigone, A. & Leo, L. (2009) Narrow band imaging in endometrial lesions. *J. Minim. Invasive Gynecol.*, **16(1)**, 9-10.
Takeuchi, M., Matsuzaki, K. & Nishitani, H. (2009) Diffusion-weighted magnetic resonance imaging of endometrial cancer: differentiation from benign endometrial lesions and preoperative assessment of myometrial invasion. *Acta Radiol.*, **50**, 947-953.
Tamai, K., Koyama, T., Saga, T., Umeoka, S., Mikami, Y., Fujii, S. & Togashi, K. (2007) Diffusion-weighted MR imaging of uterine endometrial cancer. *J. Magn. Reson. Imaging*, **26**, 682-687.
Tinelli, R., Surico, D., Leo, L., Pinto, V., Surico, N., Fusco, A., Cicinelli, M.V., Meir, Y.J. & Cicinelli, E. (2011) Accuracy and efficacy of narrow-band imaging versus white light hysteroscopy for the diagnosis of endometrial cancer and hyperplasia: a multicenter controlled study. *Menopause*, **18**, 1026-1029.
Trimble, C.L., Kauderer, J., Zaino, R., Silverberg, S., Lim, P.C., Burke, J.J. 2nd., Alberts, D. & Curtin, J. (2006) Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. *Cancer*, **106**, 812-819.
Widra, E.A., Dunton, C.J., McHugh, M. & Palazzo, J.P. (1995) Endometrial hyperplasia and the risk of carcinoma. *Int. J. Gynecol. Cancer*, **5**, 233-235.
Xie, X., Lu, W.G., Ye, D.F., Chen, H.Z. & Fu, Y.F. (2002) The value of curettage in diagnosis of endometrial hyperplasia. *Gynecol. Oncol.*, **84**, 135-139.

Prospective Study of Sentinel Lymph Node Biopsy Without Further Pelvic Lymphadenectomy in Patients With Sentinel Lymph Node–Negative Cervical Cancer

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Objective: The aim of the present study was to evaluate the incidence of lymphedema and cancer recurrence rate in patients with cervical cancer who undergo sentinel lymph node (SLN) biopsy alone in the absence of SLN metastases.

Patients and Methods: The study included 35 consecutive patients with cervical cancer scheduled for radical hysterectomy at Tohoku University Hospital between May 2006 and July 2009. All patients had International Federation of Gynecology and Obstetrics stages IA1 to IIA1 disease. Patients in whom SLNs were detected unilaterally or not detected and/or whose lymph nodes were diagnosed intraoperatively as positive metastasis underwent systemic pelvic lymphadenectomy. Patients who were found negative for SLN metastasis did not undergo further pelvic lymphadenectomy.

Results: The mean number of detected SLNs was 4.1 (range, 1–11). True lymph node metastasis could be detected in 11 (31%) of the 35 cases. Intraoperative frozen section identified correctly in 8 of 11 metastatic patients. Twenty-three patients underwent SLN biopsy alone without systematic pelvic lymphadenectomy. None of the 23 patients diagnosed with negative SLNs have experienced a lymph node recurrence in the pelvic cavity. New symptomatic lower extremity lymphedema was identified in 2 (8.7%) of the 23 patients who underwent SLN biopsy alone and in 5 (42%) of 12 patients who underwent systematic lymphadenectomy.

Conclusion: Radical hysterectomy with SLN biopsy alone seems to be a safe and effective strategy for detection of lymph node metastasis and for reducing the number of patients with lower extremity lymphedema, but a more convenient and sensitive procedure for intraoperative diagnosis needs to be established.

Key Words: Sentinel lymph node (SLN), Cervical cancer, 99mTc phytate, Micrometastasis, Lymphedema

Received April 19, 2012, and in revised form June 1, 2012.
Accepted for publication June 10, 2012.

(*Int J Gynecol Cancer* 2012;22: 1244–1250)

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ISSN: 1048-891X
DOI: 10.1097/IGC.0b013e318263f06a

This work was supported by a Grant-in-Aid from the Kurokawa Cancer Research Foundation; a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Science and Culture, Japan; a Grant-in-Aid from the Ministry of Health, Labor and Welfare, Japan; and the 21st Century COE Program Special Research Grant (Tohoku University) from the Ministry of Education Science, Sports and Culture, Japan.
The authors declare no conflicts of interest.

The number of young women with cervical cancer has increased in recent years.[1] Such patients must survive with treatment-associated sequelae for a long time. Therefore, prevention of some of these sequelae, particularly lymphedema, is important in this patient population.[2] In breast cancer, the rate of postoperative complications including lymphedema has been reported to significantly decrease in patients who undergo sentinel lymphadenectomy alone.[3]

The feasibility of sentinel lymph node (SLN) mapping for staging of gynecological malignancies has been well explored in vulvar cancer,[4,5] cervical cancer,[6–10] and endometrial cancer.[11–13] In cervical cancer, a review of 842 patients in whom SLN mapping was performed revealed a 97% detection rate and 92% sensitivity when a combined method (both radioactive tracer and blue tracer) was used.[8] Moreover, multicenter studies have reported that SLN detection is fully reliable when SLNs are detected bilaterally.[7,10] In breast cancer, a randomized controlled study demonstrated that SLN biopsy is an effective and well-tolerated procedure.[14] However, the rates of cancer recurrence and lymphedema occurrence in patients with SLN-negative cervical cancer who do not undergo further pelvic lymphadenectomy are thus far unknown.

Our previous report described the use of an SLN identification technique using technetium-99mTc phytate and patent blue dye injection in cervical cancer.[6] Moreover, another study demonstrated that only SLNs, and not nonsentinel nodes, had micrometastases and/or isolated tumor cells (ITCs) in patients with cancer cells.[15] The aim of the present study was to evaluate the incidence of lymphedema and cancer recurrence rate in patients who undergo SLN biopsy alone in the absence of SLN metastases.

MATERIALS AND METHODS

Patients

Consecutive patients with cervical cancer included in this study were treated at Tohoku University Hospital between May 2006 and July 2009 after signing a full, written, informed consent form. The study protocol was approved by the Ethics Committee of Tohoku University Graduate School of Medicine, Sendai, Japan (2005–279). Patients with International Federation of Gynecology and Obstetrics stage IA1 (with severe lymphovascular space involvement), IA2, IB1, or IIA1 disease were eligible for study participation. Exclusion criteria included evidence of lymph node metastases and/or tumors more than 3 cm on magnetic resonance imaging (MRI) and/or computed tomography at preoperative evaluation. Patients underwent laparotomy (radical hysterectomy for stages IA2 to IIB1 disease and extended hysterectomy for stage IA1 disease, with or without pelvic lymphadenectomy) with SLN biopsy. Patients in whom SLNs were detected unilaterally or not detected and/or who had a diagnosis of positive lymph node metastasis intraoperatively underwent systemic pelvic lymphadenectomy. Patients who were found negative for SLN metastasis did not undergo further pelvic lymphadenectomy. Adjuvant therapy was performed according to final pathological results after surgery. The present study flow is summarized in Figure 1.

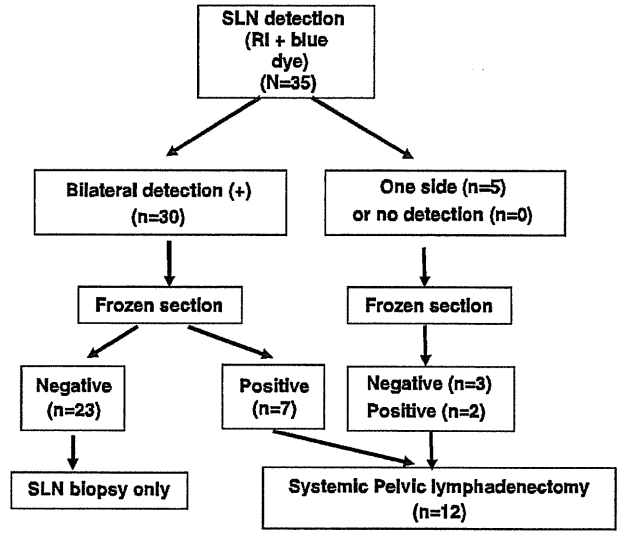

FIGURE 1. Distribution of patients in the present study (flowchart).

SLN Detection Procedure

The SLN detection procedure described in our previous report[6] was followed. On the day before surgery, lymphoscintigraphy was performed with injection of 0.4 mL of fluid containing 60 MBq 99mTc-labeled phytate (DRL, Tokyo, Japan) into the cervix at the 3-, 6-, 9-, and 12-o'clock positions (0.1 mL per injection site). These procedures were conducted in the nuclear medicine department. Dynamic lymphoscintigraphy lasted for approximately 1 hour. The first lymphoscintigram was taken at this time, and the second lymphoscintigram was taken the next morning just before the patient entered the operating room.

After the abdominal cavity was opened, 4.0 mL of blue dye (patent blue violet; Sigma, St Louis, MO) was injected into the cervix (1.0 mL per injection site) at the same sites as the radioisotope-phytate solution. Before lymphadenectomy was started, radioactive and/or blue lymph node(s) were located using a gamma-detecting probe (Navigator GPS, RMD; Watertown, MA) and by inspection, respectively. When the gamma-detecting probe registered counts of more than 10-fold higher than background radiation levels, the node was considered radioactive. All radioactive and blue nodes were considered SLNs. After SLN biopsy was performed, the area of lymphadenectomy was scanned with the probe to confirm that no radioactive tissue remained. One surgeon conducted all the sentinel node biopsies and other surgical procedure. We had experienced SLN biopsies for more than 50 patients with cervical cancer for 5 years before the present study. Areas of detection of SN are expressed using international surgical classification as those proposed by Cibula and Abu-Rustum.[16]

Pathological Examination

Frozen section analysis of detected SLNs was performed intraoperatively. Each SLN was examined using step sectioning at 2-mm intervals parallel to the short axis of

the node and examined with hematoxylin and eosin (H&E) staining. The remaining tissue was fixed in formalin and embedded in paraffin for routine histological analysis.

All surgically removed non-SLNs were examined histopathologically using routine H&E staining. After SLNs were reexamined and diagnosed as negative for metastasis by routine H&E staining, the blocks were cut at 0.1-mm intervals, and slides were immunostained with an antibody directed against cytokeratin (AE1/AE3, Dako, Japan), expression of which is a characteristic of metastatic cancer cells.

Isolated tumor cells were defined as metastases measuring 0.2 mm or less. Micrometastases were defined as tumors ranging from 0.2 to 2 mm. Tumors more than 2 mm were defined as macrometastases.[17]

Follow-up

Patients were followed up every 1 to 3 months for 4 years and then every 6 months. At each follow-up visit, pelvic examination, ultrasonography (USG), and vaginal cytology were performed. Computed tomography and/or MRI were performed every 1 year or in the case of clinical suspicion. The presence of lymphedema and/or phlegmon was documented, and those symptoms were evaluated through the follow-up period. Lower extremity lymphedema was judged based on the consensus document of the International Society of Lymphology.[18] Stage I represents swelling caused by fluid relatively high in protein content and subsides with limb elevation. Pitting may occur. Stage II signifies that limb elevation alone rarely reduces tissue swelling, and pitting is manifest. Late in stage II, the limb may or may not pit as tissue fibrosis supervenes. Stage III encompasses lymphostatic elephantiasis, where pitting is absent and skin changes such as acanthosis, fat deposits, and warty overgrowths develop. In the present study, lymphedema was defined as stage II or III cases related to lymphadenectomy.

Statistical Analyses

The Fisher exact test was used to test differences between the methods for statistical significance in case of 2×2 tables and the χ^2 test in case of $2 \times \kappa$ tables. $P < 0.05$ was considered statistically significant.

RESULTS

Patients' Characteristics

Patients' ages ranged from 24 to 62 years (median, 39 years). Conization was performed in 18 patients before radical hysterectomy. Histological analysis revealed squamous cell carcinoma in 29 patients and adenocarcinoma in 6 patients. International Federation of Gynecology and Obstetrics stages included IA1 (n = 2), IA2 (n = 2), IB1 (n = 29), and IIA1 (n = 2). Only 2 patients had a tumor of more than 2 cm in diameter: patient 10 had a tumor with a diameter of 3 cm, whereas the diameter of the tumor in patient 12 was determined as 4 cm after surgery.

Detection Rates and Sites of SLNs

Results of SLN detection are summarized in Table 1. The mean number of detected SLNs was 4.1 (range, 1–11). Most patients had an SLN in one of the following 3 sites: obturator region (62 nodes), external iliac region (33 nodes), and internal iliac region (26 nodes). Intraoperative scanning with a gamma probe detected at least one hot spot in all patients (100%). Bilateral SLNs were detected in 30 (86%) of the 35 patients.

Lymph Node Metastasis

Sizes and locations of lymph node metastasis are summarized in Table 1. Sentinel lymph nodes in 9 patients were diagnosed as positive intraoperatively, but the SLN in case 17 was determined to be false positive. The histologic classification of case 17 was adenocarcinoma, and endosalpingiosis was misdiagnosed as a metastasis in frozen sections. Sentinel lymph node metastasis was detected postoperatively in case 11 (squamous cell carcinoma) and case 22 (adenocarcinoma) as micrometastasis and in case 7 as ITCs of squamous cell carcinoma. Sentinel lymph node micrometastasis was found by postoperative reexamination of intraoperative frozen sections in case 11 and by postoperative reexamination using sectioning at 0.1-mm intervals in case 22. The left external iliac lymph node was swollen, and metastasis was detected by intraoperative biopsy in case 18. No SLN could be detected on the left side of the pelvic cavity, but micrometastasis was detected in the right external SLN. True lymph node metastasis was detected in 11 (31%) of the 35 cases. Intraoperative frozen section identified correctly in 8 of the 11 patients with metastasis.

Surgical Procedure and Adjuvant Therapy

Surgical procedures and adjuvant therapy are summarized in Table 2. Twenty-three patients underwent SLN biopsy alone without systematic pelvic lymphadenectomy. Overall, 7 patients with positive SLN metastasis and 5 patients without bilateral SLN detection underwent systematic pelvic lymphadenectomy.

Nine of the 23 patients who underwent SLN biopsy alone received adjuvant chemoradiation or radiation therapy, whereas 8 of 12 patients who underwent systematic lymphadenectomy received adjuvant chemoradiation therapy. Concurrent chemoradiotherapy was indicated to patients with positive lymph node metastasis and/or with severe lymphovascular invasion, and radiation therapy was indicated for patients with deep stromal invasion in the present study.

The median operation time was 190.5 minutes (range, 153–302 minutes) in the systematic lymphadenectomy group and 198 minutes (range, 127–286 minutes) in the SLN biopsy alone group. The median amount of blood loss was 598.5 mL (range, 86–1142 mL) in the systematic lymphadenectomy group and 415 mL (range, 152–1576 mL) in the SLN biopsy alone group.

Follow-Up

The median follow-up period for all 35 patients was 49 months (range, 15–70 months), with a minimum of 32 months in survivors. Of the 35 patients, 34 are alive and 31 have experienced no recurrence. None of the 23 patients with negative SLNs have experienced a lymph node recurrence in the pelvic cavity, although 3 patients have experienced a cancer recurrence: lung metastasis in patients 13 and 26

TABLE 1. Sentinel lymph node characteristics

Case Number	No. SLN		Detection Site		SLN Met Detection	
	R	L	R	L	Intraop	Postop
1	1	1	Ext	Obt	–	–
2	3	3	Com, Int	Int, Obt	–	–
3	1	1	Ext	Obt	Macro	
4	1	1	Int	Obt	–	–
5	3	1	Ext, Obt	Int	–	–
6	4	2	Ext, Com, Int	Ext	–	–
7	1	4	Obt	Obt	–	ITCs
8	1	0	Obt		–	–
9	1	3	Int	Int	–	–
10	3	1	Obt	Obt	–	–
11	2	2	Ext, Obt	Ext	–	Micro
12	2	1	Ext, Obt	Obt	Macro	
13	1	2	Obt	Obt, Int	–	–
14	4	6	Ext, Obt, Int	Ext, Obt, Int, Com	Micro	
15	1	2	Com	Com, Sac	–	–
16	1	0	Sac		–	–
17	3	1	Obt, Int	Int	Micro*	
18	1	0	Ext		Micro	
19	1	1	Ext	Ext	–	–
20	2	1	Ext	Ext	–	–
21	2	2	Obt	Obt, Ext	Micro	
22	2	2	Obt, Int	Obt	–	Micro
23	4	1	Int, Pa	Obt	Macro	
24	8	1	Pa, Com, Obt, Ext	Ext	–	–
25	1	0	Int		–	–
26	4	1	Int, Obt, Sac	Obt	–	–
27	4	3	Pa, Obt, Ext	Sac, Obt	Macro	
28	1	5	Obt	Obt, Com	–	–
29	2	1	Ext, Pa	Pa	–	–
30	1	1	Ext	Ext	–	–
31	1	1	Ext	Ext	–	–
32	1	2	Ext	Sac, Int	–	–
33	2	5	Obt	Int	–	–
34	4	7	Obt, Ext, Com	Obt, Ext	–	–
35	4	0	Obt		ITC	

*False-positive case.

Com, common iliac; Ext, external iliac; Int, internal iliac; Intraop, intraoperative; ITC, isolated tumor cell; L, Left; Macro, macrometastasis; Met, metastases; Micro, micrometastasis; Obt, obturator; Postop, postoperative; Pa, para-aortic; R, right; Sac, sacral.

and vaginal metastasis in patient 19; both of these patients received additional therapy and are currently alive with no evidence of disease. Patient 12 underwent standard radical hysterectomy owing to the presence of SLN metastasis detected intraoperatively and subsequently received adjuvant chemoradiation therapy; however, she experienced recurrence and died 15 months after surgery.

Therapeutic characteristics and adverse effects are summarized in Table 2. New symptomatic lower extremity lymphedema was identified in 2 (8.7%) of 23 patients who underwent SLN biopsy alone. In contrast, 5 (42%) of 12 patients with systematic lymphadenectomy experienced leg edema. The incidence of lower extremity lymph edema was significantly lower ($P = 0.03$) in the SLN biopsy alone group

TABLE 2. Therapeutic characteristics and adverse effects

Case Number	Lymph Node Dissection	Adjuvant	Lymphedema	Lymphocyst
1	SLNB	−	−	−
2	SLNB	−	−	−
3	PLA	Chemorad	−	+
4	SLNB	Chemorad	−	−
5	SLNB	Chemorad	−	−
6	SLNB	−	−	−
7	SLNB	Chemorad	−	−
8	PLA	−	+	−
9	SLNB	−	−	−
10	SLNB	Rad	−	−
11	SLNB	−	+	+
12	PLA	Chemorad	−	−
13	SLNB	−	−	−
14	PLA	Chemorad	+	−
15	SLNB	−	−	−
16	PLA	−	−	−
17	PLA	−	+	−
18	PLA	Chemorad	−	−
19	SLNB	−	−	−
20	SLNB	−	−	−
21	PLA	Chemorad	+	−
22	SLNB	Chemorad	−	−
23	PLA	chemorad	−	−
24	SLNB	−	−	−
25	PLA	−	−	−
26	SLNB	Rad	−	−
27	PLA	Chemorad	+	−
28	SLNB	−	−	−
29	SLNB	−	−	−
30	SLNB	−	−	−
31	SLNB	Chemorad	+	−
32	SLNB	−	−	−
33	SLNB	Rad	−	−
34	SLNB	Rad	−	−
35	PLA	Chemorad	−	−

Chemorad, concurrent chemoradiotherapy; PLA, pelvic lymphadenectomy; Rad, radiation therapy; SLNB, SNL biopsy.

than in the systematic lymphadenectomy group. The incidence of lymphocyst was identified in 1 patient of both groups.

DISCUSSION

Sentinel lymph node dissection has become a standard of care in patients with breast cancer and melanoma.[14,19] In cervical cancer, several reports have evaluated the feasibility of SLN biopsy, and the detection rate and accuracy results were not inferior to those of breast cancer.[6–10] We also previously studied the feasibility of SLN detection in patients with cervical cancer and reported that micrometastases could be detected by step-serial sectioning with cytokeratin immunostaining.[6,15] To our knowledge, only one prospective study about patients with cervical cancer managed using SLN biopsy without further systematic pelvic lymphadenectomy has been published, but it did not report on lymphedema incidence.[9] The present study is the first prospective study to evaluate the safety of a strategy in which patients without SLN metastasis undergo no further pelvic lymphadenectomy, and to compare

the incidence of lymphedema between patients who undergo SLN biopsy alone versus SLN biopsy followed by pelvic lymphadenectomy.

An AGO group study reported a 94% SLN detection rate in patients with tumors less than 2 cm.[7] Only 2 patients had a tumor with a diameter of more than 2 cm in our study, in whom the SLN detection rate was 100% and bilateral detection rate was 84%. Patients with such a small tumor size may be adequately treated with SLN biopsy.

In the present study, patients in whom SLNs could not be detected bilaterally and/or who were diagnosed with positive lymph node metastasis intraoperatively underwent systematic (bilateral) pelvic lymphadenectomy. The previous literature has indicated that no false-negative results have been observed in patients in whom SLNs were identified bilaterally.[10] In patient 18, only the right external SLN could be detected, in which micrometastasis was identified, but a lymph node with macrometastasis on the left side was not recognized as an SLN. The other 4 patients in whom unilateral SLNs were detected did not have lymph node metastasis in non-SLNs.

To date, even if patients have proven to have swollen and/or metastatic lymph nodes intraoperatively and the therapeutic efficacy of removal of metastatic SLNs has been unclear, we have performed radical hysterectomy with pelvic lymphadenectomy. Although avoidance of unilateral pelvic lymphadenectomy in patients without SLN metastasis on the same side may be safe, this remains unclear. We classified patients in whom SLNs could not be detected bilaterally as failures and thus moved forward with bilateral lymphadenectomy. Further study to identify patients in whom unilateral pelvic lymphadenectomy can be avoided is required.

Lymph node metastasis was detected in 11 (31%) of the 35 patients in the present study. Ultrastaging using SLN biopsy has been previously reported to improve identification of lymph node metastasis in patients with cervical cancer[20]; the lymph node metastasis detection rate has been reported to be almost 20%.[21] Moreover, the detection rate of micrometastasis has been reported to be higher than that of SLN biopsy.[21] The present study included 4 patients with micrometastasis and 2 patients with ITCs. In patients with squamous cell carcinoma, all metastases except for ITCs should be identified using intraoperative frozen sectioning. Intraoperative 2-mm interval step-serial sectioning in squamous cell carcinoma is considered a safe method for identifying lymph nodes with more than 0.2-mm metastases, although intraoperative diagnosis is not precise and not recommended by some researchers.[22] In contrast, benign type inclusions, such as endosalpingiosis and endometriosis, are frequently encountered in pelvic lymph nodes of women; and endosalpingiosis has been reported to lead to misdiagnosis in adenocarcinoma cases.[23] Moreover, sensitivity to radiation therapy is relatively high in patients with squamous cell carcinoma compared to those with adenocarcinoma.[24] Thus, careful diagnosis is necessary in cervical adenocarcinoma. It may be safe to recommend avoiding systematic pelvic lymphadenectomy only in patients with squamous cell carcinoma.

In the present study, each SLN was examined using step sectioning at 2-mm intervals parallel to the short axis of the node. The improvement in detection of lymph node metastasis compared to that of past reports may be that a larger number of frozen sections were diagnosed intraoperatively. Whereas the detection rate of lymph node metastasis has improved, the workload of pathologists has also increased. Thus, the ability to perform the present intraoperative diagnostic procedure may be limited in some institutions. Other convenient strategies for intraoperative diagnosis, such as mRNA detection and one-step nucleic acid amplification techniques, need to be established.[25] Regardless of the method used, SLN diagnosis should be performed by a fully trained pathologist.

In the present study, micrometastasis was detected in 4 patients, macrometastasis was detected in 5 patients, and ITCs were detected in 2 patients. No patients, except for patients 12, had lymph node metastasis in a non-SLN among the 8 cases diagnosed as positive SLN metastasis intraoperatively. Patient 12 had SLN metastasis at the right obturator basin but also had a macroscopically swollen and metastatic lymph node at the right external iliac basin that was not detected as a SLN. We do not know whether a strategy is feasible in which systematic lymphadenectomy is skipped and adjuvant therapy is administered in cases with micrometastasis only. Future evaluation is required to confirm the safety of this procedure.

New symptomatic lower extremity lymphedema was identified in only 2 patients (patients 11 and 31) with SLN biopsy alone. The incidence of lower extremity lymph edema was significantly lower in the SLN biopsy alone group than in the systematic lymphadenectomy group. Four SLNs (one right external node, one obturator node, and 2 left external nodes) were removed, and no further radiation therapy was needed for patient 11. Two SLNs (bilateral external nodes) were removed and chemoradiation therapy was performed on patient 31 with parametrial lymphovascular invasion. In breast cancer, lymphedema appeared in 5% of the SLN biopsy alone patients, compared with 16% of the patients with systematic lymphadenectomy.[3] In cervical cancer, we suspect that the occurrence of lymphedema has low frequency but nearly the same frequency as that in the patients with breast cancer even if only SLN biopsy is performed.

In conclusion, SLN biopsy without further pelvic lymphadenectomy in patients with SLN-negative cervical cancer may be safe, particularly in patients with squamous cell carcinoma who can receive potentially effective radiation therapy and effective for preventing extremity lymphedema. A more convenient and sensitive procedure for intraoperative diagnosis needs to be established. The 5-year survival rate is high (approximately 95%) in patients with IB1 cervical cancer who underwent radical hysterectomy with systematic lymphadenectomy. Such patients represent the target of SLN biopsy. If a randomized trial is powered to test noninferiority (a difference in survival of 5% between the SLN only and full lymph node dissection groups at 5 years), more than 640 patients are required to obtain 80% power with a 1-sided α equal to 0.05. Therefore, a randomized controlled trial with patient survival as an outcome would not be feasible; rather, observational prospective specialized multicenter trials are required in the future. Moreover, lymphedema occurrence or lymph node metastases seem to be useful end points. Our

present study was a nonrandomized study, and the number of evaluable patients was small. The use of SLN biopsy without full lymph node dissection may be demonstrated in the randomized study (Ganglion Sentinell dans Cancer du Col 2) that is ongoing in France, in which incidence of adverse events is the primary outcome.

ACKNOWLEDGMENTS

The authors thank Miss Keiko Abe and Miss Emi Endo for preparing material.

REFERENCES

1. Kokawa K, Takekida S, Kamiura S, et al. The incidence, treatment and prognosis of cervical carcinoma in young women: a retrospective analysis of 4,975 cases in Japan. *Eur J Gynaecol Oncol.* 2010;31:37–43.
2. Ohba Y, Todo Y, Kobayashi N, et al. Risk factors for lower-limb lymphedema after surgery for cervical cancer. *Int J Clin Oncol.* 2011;16:238–243.
3. McLaughlin SA, Wright MJ, Morris KT, et al. Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: objective measurements. *J Clin Oncol.* 2008;26:5213–5219.
4. Moore RG, Robison K, Brown AK, et al. Isolated sentinel lymph node dissection with conservative management in patients with squamous cell carcinoma of the vulva: a prospective trial. *Gynecol Oncol.* 2008;109:65–70.
5. Hampl M, Hantschmann P, Michels W, et al. Validation of the accuracy of the sentinel lymph node procedure in patients with vulvar cancer: results of a multicenter study in Germany. *Gynecol Oncol.* 2008;111:282–288.
6. Niikura H, Okamura C, Akahira J, et al. Sentinel lymph node detection in early cervical cancer with combination 99mTc phytate and patent blue. *Gynecol Oncol.* 2004;94:529–532.
7. Altgassen C, Hertel H, Brandstadt A, et al. AGO study group. Multicenter validation study of the sentinel lymph node concept in cervical cancer: AGO Study Group. *J Clin Oncol.* 2008;26:2943–2951.
8. van de Lande J, Davelaar EM, von Mensdorff-Pouilly S, et al. Sentinel lymph node detection in early stage uterine cervix carcinoma: a systematic review. *Gynecol Oncol.* 2007;106:604–613.
9. Gortzak-Uzan L, Jimenez W, Nofech-Mozes S, et al. Sentinel lymph node biopsy vs. pelvic lymphadenectomy in early stage cervical cancer: is it time to change the gold standard? *Gynecol Oncol.* 2010;116:28–32.
10. Lecuru F, Mathevet P, Querleu D, et al. Bilateral negative sentinel nodes accurately predict absence of lymph node metastasis in early cervical cancer: results of the SENTICOL study. *J Clin Oncol.* 2011;29: 1686–1691.
11. Niikura H, Okamura C, Utsunomiya H, et al. Sentinel lymph node detection in patients with endometrial cancer. *Gynecol Oncol.* 2004;92:669–674.
12. Khoury-Collado F, Murray MP, Hensley ML, et al. Sentinel lymph node mapping for endometrial cancer improves the detection of metastatic disease to regional lymph nodes. *Gynecol Oncol.* 2011;122:251–254.
13. Ballester M, Dubernard G, Lécuru F, et al. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO). *Lancet Oncol.* 2011;12:469–476.
14. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA.* 2011;305:569–575.
15. Okamoto S, Niikura H, Yoshinaga K, et al. Detection of micrometastases in cervical cancer with a system that evaluates both sentinel and nonsentinel lymph nodes. *Int J Gynecol Cancer.* 2009;19:708–711.
16. Cibula D, Abu-Rustum NR. Pelvic lymphadenectomy in cervical cancer—surgical anatomy and proposal for a new classification system. *Gynecol Oncol.* 2010;116:33–37.
17. Hermanek P, Hutter RV, Sobin LH, et al. International Union Against Cancer: classification of isolated tumor cells and micrometastasis. *Cancer.* 1999;86:2668–2673.
18. International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema. Consensus document of the International Society of Lymphology. *Lymphology.* 2003;36:84–91.
19. Dummer R, Hauschild A, Guggenheim M, et al; ESMO Guidelines Working Group. Melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2010;21:v194–v197.
20. Bats AS, Clement D, Larousserie F, et al Sentinel lymph node biopsy improves staging in early cervical cancer. *Gynecol Oncol.* 2007;105:189–193.
21. Bézu C, Coutant C, Ballester M, et al. Ultrastaging of lymph node in uterine cancers. *J Exp Clin Cancer Res.* 2010;29:5.
22. Fader AN, Edwards RP, Cost M, et al: Sentinel lymph node biopsy in early-stage cervical cancer: utility of intraoperative versus postoperative assessment. *Gynecol Oncol.* 2008;111:13–17.
23. Yamashita T, Katayama H, Kato Y, et al. Management of pelvic lymph nodes by sentinel node navigation surgery in the treatment of invasive cervical cancer. *Int J Gynecol Cancer.* 2009;19:1113–1118.
24. Landoni F, Maneo A, Colombo A, et al. Randomized study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. *Lancet.* 1997;350:535–540.
25. Tsujimoto M, Nakabayashi K, Yoshidome K, et al. One-step nucleic acid amplification for intraoperative detection of lymph node metastasis in breast cancer patients. *Clin Cancer Res.* 2007;13:4807–4816.

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Small Cell Carcinoma of the Uterine Cervix: Clinical Outcome of Concurrent Chemoradiotherapy with a Multidrug Regimen

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Small cell carcinoma of the uterine cervix (SCCC) is a rare subtype of cervical cancer with an aggressive behavior. Although SCCC has a worse prognosis than other histological types of uterine cervical cancer such as squamous cell carcinoma or adenocarcinoma, standard therapy for SCCC remains to be established due to its rarity. The purpose of this study was to evaluate the efficacy and toxicity of concurrent chemoradiotherapy (CCRT) using a regimen consisting of vincristine, adriamycin, and cyclophosphamide alternating with cisplatin and etoposide (VAC/PE). We analyzed a series of 9 patients with SCCC. Five patients with stage IB disease underwent radical hysterectomy followed by CCRT. Four patients with advanced stage disease received CCRT primarily. With a median follow-up duration of 47.4 months (range, 10.5 to 86.4 months), 4 out of 5 patients with stage IB disease were alive without recurrence. In 4 patients with advanced stage disease, the response rate was 75% (complete response, 1; partial response, 2; progressive disease, 1). One patient with stage IVB disease remained without recurrence for 89.5 months. At 5 years, overall survival (OS) and progression-free survival for all patients was 52% and 56%, respectively. Patients with early-stage disease had an 80% 5-year OS rate compared to 25% for patients with advanced stage disease. Although all patients developed grade 3-4 neutropenia, CCRT using VAC/PE is feasible in both the primary and adjuvant settings for SCCC. In particular, this combined modality therapy may improve both local control and survival as postoperative treatment in patients with early-stage disease.

Keywords: concurrent chemoradiotherapy; neuroendocrine carcinoma; small cell carcinoma of the uterine cervix; uterine cervical cancer; VAC/PE

Tohoku J. Exp. Med., 2013 Jan, **229** (1), 75-81.

Cervical cancer is the 5th most common cancer among women in Japan; the mortality from cervical cancer in 2010 was 4.1 per 100,000 female population (Matsuda et al. 2011). Cervical cancer encompasses several histologic types, of which squamous cell carcinoma (SCC) is the most common histologic subtype accounting for 70-80% of invasive carcinomas. Adenocarcinoma (AC) and adenosquamous carcinoma comprise 10-15% of all cases (Kurman et al. 2011).

Cervical neuroendocrine tumors are uncommon and four categories include: (1) typical carcinoid tumor, (2) atypical carcinoid tumor, (3) large cell neuroendocrine carcinoma, and (4) small cell carcinoma. Small cell carcinoma of the uterine cervix (SCCC), which was first described in 1957, accounts for only 1% of uterine cervical cancers and is an extremely aggressive subtype of uterine cervical cancer (Tsunoda et al. 2005; Crowder and Tuller 2007; Agarwal et al. 2011). Compared to the more common squamous cell carcinoma of the cervix, SCCC is more likely to show lymphovascular invasion, metastasize to the lymph nodes, and recur. Looking at the prognosis by histological subtype, 5-year overall survivals (OS) of SCC and AC are 70.5% and 68.7%, respectively (Quinn et al. 2006). The 5-year survival rate for SCCC ranges from 32% (n = 25) to 36.8% (n = 135), even for patients with early-stage disease (Chan et al. 2003; Cohen et al. 2010). Survival following radical hysterectomy without adjuvant therapy is worse than that of non-SCCC of comparable stage (5-year disease-free survival: SCCC [n = 11], 36% vs. non-SCCC [n = 301], 71%) (Sevin et al. 1996). Given the poor prognosis, it is important to establish standard, effective therapy for SCCC.

Small cell carcinoma occurs most frequently in the lung, and the clinical and biologic characteristics of small cell lung cancer (SCLC) are distinct from those of non-

Received September 6, 2012; accepted December 11, 2012. Published online December 27, 2012; doi: 10.1620/tjem.229.75.

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SCLC. SCLC exhibits aggressive behavior, with rapid growth, early spread to distant sites, and sensitivity to chemotherapy and radiation. Because SCCC is rare, the therapeutic strategies used for SCLC can offer valuable information that may contribute to the establishment of standard therapy for SCCC. Although irradiation improves both the local control and survival rates in SCLC patients (Warde and Payne 1992), chemotherapy has historically been the cornerstone of SCLC management. Chang et al. attempted to treat SCCC in a fashion similar to that used in SCLC, and reported a 5-year overall survival (OS) of 68% (n = 28) for patients treated with vincristine, adriamycin, and cyclophosphamide alternating with cisplatin and etoposide (VAC/PE) compared to 33% (n = 12) for patients who received a regimen consisting of cisplatin, vinblastine, and bleomycin (Chang et al. 1998). In another small phase II trial of alternating VAC/PE in early-stage SCCC before hysterectomy, 6 of 7 patients experienced a clinical complete response (CR) (Chang et al. 1999). Hoskins et al. (1995) reported that while radiotherapy with concurrent chemotherapy using the PE regimen was effective for locally advanced disease (n = 11; 3-year OS, 28%), it was inadequate to control systemic disease. We therefore adopted a protocol of CCRT using the alternating VAC/PE regimen in an effort to improve outcomes at our center.

In this study, we evaluated the efficacy and toxicity of CCRT using the alternating VAC/PE regimen and analyzed progression-free survival (PFS) and overall survival in patients with SCCC.

Materials and Methods

Patients

Eligible patients were required to have histologically confirmed small cell carcinoma in the cervix. Histopathologic diagnosis was based on morphologic criteria following hematoxylin-eosin (H-E) staining (Albores-Saavedra et al. 1997; Ishida et al. 2004; Katahira et al. 2004). The morphologic criteria included the presence of small cells with hyperchromatic nuclei and scanty cytoplasm, absent or inconspicuous nucleoli, and numerous mitotic figures and extensive necrosis. Nine patients received the diagnoses of SCCC from January 2001 to December 2009. Of the nine patients, five patients were diagnosed with immunohistochemistry as shown in Table 1.

All tumors were staged according to the International Federation of Gynecology and Obstetrics (FIGO) 2008 classification system for cervical cancer, based on physical examination. Early stage was defined as Stages I-IIA and advanced as Stages IIB-IVB. Five patients with FIGO stage IB1 or IB2 underwent hysterectomy and pelvic lymphadenectomy. Four patients with advanced stage disease underwent CCRT. All patients had neither previous chemotherapy nor irradiation. Patients also had adequate hematological and hepatic function parameters, and an Eastern Cooperative Oncology Group performance status of two or less. All of the patients were informed that there was no standard chemotherapy regimen for SCCC and that VAC/PE was a favorable regimen for SCCC based on the reports by Chang et al (Chang et al. 1999). This study to analyze the case series was approved as a retrospective study by our institutional review board.

Treatment

As primary treatment, stage IB-IIA patients underwent radical hysterectomy (type III or type II) and pelvic lymphadenectomy. Subsequently, external beam pelvic radiotherapy (EBRT) was initiated within six weeks of surgery. EBRT was delivered to a total dose of 45-50 Gy in 23-25 daily fractions over five to six weeks. Tumor-directed radiation was utilized in one patient in whom a metastatic lymph node was not resected (Patient #8). Concurrent chemotherapy was administered within a week after initiating radiotherapy, with 3 cycles every 6 weeks as follows: intravenous infusion of 1 mg/m^2 of vincristine, 40 mg/m^2 of adriamycin and 1,000 mg/m^2 of cyclophosphamide, day 1; intravenous infusion of 100 mg/m^2 of cisplatin, day 22; 100mg/m^2 of etoposide, day 22-24. Cycles were delayed for adverse events as defined by the Common Toxicity Criteria (CTC) grade 2 or greater, neutropenia < 1,500 per ul or thrombocytopenia < 100,000 per ul. The dose of each drug was reduced by 25% of the previous dose in the case of grade 3/4 toxicities.

For advanced-stage disease, the initial 20 Gy was delivered to the

Table 1. Patient Characteristics.

Patient no.	Age	Type of SCCC	IHC					FIGO stage	T	N	M	Tumor size (cm)	Site of metastasis	PS
			NSE	CGA	Synaptophysin	NCAM	CD56							
1	28	pure	N/D	N/D	N/D	N/D	N/D	IVb	3b	1	1	5	lung	0
2	44	pure	N/D	N/D	N/D	N/D	N/D	IVb	3b	1	1	5	lt. infraclavilular LN	0
3	34	pure	N/D	N/D	N/D	N/D	N/D	IIb	2b	1	0	8	none	0
4	61	pure	positive	positive	positive	N/D	positive	IIb	2b	0	0	6	none	0
5	31	pure	N/D	positive	N/D	positive	N/D	Ib1	1b1	1	0	2	none	0
6	39	mixed	positive	negative	negative	positive	N/D	Ib2	1b2	1	0	8	none	0
7	44	pure	N/D	N/D	N/D	N/D	N/D	Ib2	1b2	1	0	6	none	0
8	59	mixed	positive	negative	positive	N/D	positive	Ib1	1b1	0	0	3	none	0
9	40	pure	positive	positive	positive	positive	N/D	Ib1	1b1	0	0	2	none	0

mean 42

SCCC, small cell carcinoma of the uterine cervix; IHC, immunohistochemistry; NSE, Neuron-specific enolase; CGA, Chromogranin A; NCAM, Neural cell adhesion molecule; N/D, not done; FIGO, International Federation of Gynecology and Obstetrics.

whole pelvis. After that, 30 Gy was administered through the same whole-pelvis field with a midline block. The first high dose-rate intracavitary brachytherapy session (6 Gy per week, 4-5 fractions) with chemotherapy was performed within 10 days after the initial 20 Gy of EBRT. The VAC/PE chemotherapy was administered concurrently with the same dose for early stage disease within a week of the initial radiotherapy. A paraaortic boost (50 Gy) was added when paraaortic lymph node metastasis was recognized by computed tomography (CT). Hysterectomy was added for residual disease by biopsy or on magnetic resonance imaging one month following the completion of primary treatment.

Clinical and pathological variables analyzed are shown in Table 1. The primary end point was any cancer-related death. All end points were calculated from the date of the start of primary treatment to death, or censored at last follow-up. The date of death was obtained from the medical records. All end points were updated in December 2011.

Efficacy assessment

Pretreatment evaluation included past medical history and physical examination, complete blood cell count with differentials, chemistry, CT scan of chest, abdomen and pelvis, chest x-ray and any other diagnostic procedures as clinically indicated. During treatment, physical examination including toxicity assessment, complete blood cell count, and chemistry were performed every week before each cycle. Appropriate imaging studies including a CT scan were used to evaluate treatment response or to document disease progression. A CT scan confirmed responses four to six weeks after the initial response documentation. Patients were assessed every month with imaging for disease progression following the completion of the chemotherapy. Responses were classified according to the RECIST criteria (Therasse et al. 2000). Progression free survival (PFS) was calculated from the first day of treatment to the date on which disease progression was first documented or the date of the last follow-up. Overall survival (OS) was calculated from the first day of treatment to the date of death or last follow-up. Toxicity was monitored according to the National Cancer Institute (NCI) CTC scale version 3.0.

Statistical Analysis

Statistical analysis was performed using JMP Pro 9.0.2 (SAS Institute Inc. North Carolina, USA). The impact of clinical and pathologic risk factors on the survival of patients with SCCC was evaluated using the Kaplan-Meier life table analyses and log-rank tests. All tests were two-tailed with P values < 0.05 were considered significant.

Results

The mean patient age at diagnosis was 42 years (range: 28-61) and all of the patients were diagnosed with SCCC by a punch biopsy. Patient characteristics are listed in Table 1. The FIGO stage distribution was as follows: three were stage IB1, two were IB2, two were stage IIB, and two were stage IVB. Three patients had a non-bulky primary tumor, with the remaining presenting with bulky disease. The therapeutic regimens and clinical outcomes for all nine patients are shown in Table 2. The patients with stage IB disease underwent a type II or type III radical hysterectomy followed by CCRT. Four patients with advanced stage disease received CCRT primarily. Patients #2 and #3 had partial responses and underwent hysterectomy after CCRT. Both of them had remains of disease at the cervix and cardinal ligament. Eight of nine patients completed three cycles of VAC/PE and radiation. Of these, three patients (#3, #5, and #8) had dose reductions of both cisplatin and etoposide at the third cycle for grade 4 bone marrow suppression. One patient (patient #7) with severe fatigue and grade 4 neutropenia received two cycles of paclitaxel and carboplatin therapy after the first cycle of VAC/PE therapy. Treatment toxicities are listed in Table 3. The highest level of toxicity at each cycle is listed. All patients had severe neutropenia (grade 3 or 4) and two patients had febrile neutropenia (22.2%). The incidence of grade 3 and 4 toxicity was as follows: anemia, 44.4%; neutropenia, 100%; thrombocytopenia, 55.5%; nausea, 11.1%. No treatment-related death occurred during therapy.

Four patients with primary CCRT were evaluable for an objective response because five patients who underwent surgery primarily had no residual tumor after surgery. With

Table 2. Therapy and outcomes.

Patient no.	Primary therapy	Radiation (Gy)	Chemo regimen	RECIST	Site of recurrence	PFS (Mo)	Outcome	OS (Mo)
1	CCRT	WP 50 + RALS 24	VAC/PE	CR	none	89.5	alive	89.5
2	CCRT→EH+BSO	WP 50 + PAN 50 + RALS 30 + neck LN 60	VAC/PE	PR	stump	6.8	death	26.3
3	CCRT→RH+BSO+PLA	WP 50 + RALS 30	VAC/PE	PR	bone marrow	1.8	death	6.0
4	CCRT	WP 50 + RALS 24	VAC/PE	PD	lung	0.4	death	24.4
5	EH+BSO+PLA→CCRT	WP 50	VAC/PE	none	none	47.3	alive	59.6
6	RH+BSO+PLA→CCRT	WP 45	VAC/PE	none	none	39.9	alive	47.4
7	RH+BSO+PLA→CCRT	WP 50	VAC/PE→TC	none	none	78.4	alive	86.4
8	RH+BSO+PLA→CCRT	WP 50 + rt. Iliac LN 10	VAC/PE	none	bone, lung, LN	5.3	death	10.5
9	RH+BSO+PLA→CCRT	WP 50	VAC/PE	none	none	17.7	alive	19.4

CCRT, concurrent chemoradiotherapy; EH, extended hysterectomy; RH, radical hhysterectomy; BSO, bilateral salpingoophorectomy; PLA, pelvic lymphadenectomy; WP, whole pelvis; RALS, Remote After loading System; LN, lymph node; PFS, progressive free survival; OS, overall survival.

Table 3. Adverse effects by treatment (NCI-CTC).

	No. of patients (n = 9)				
Grade	0	1	2	3	4
Anemia	1	0	4	3	1
Neutropenia	0	0	0	2	7
Thrombocytopenia	1	3	0	2	3
Diarrhea	2	4	3	0	0
Nausea	0	2	6	1	0
Malaise	0	2	7	0	0
Febrile neutropenia	0	0	0	2	0
Renal Insufficiency	6	3	0	0	0

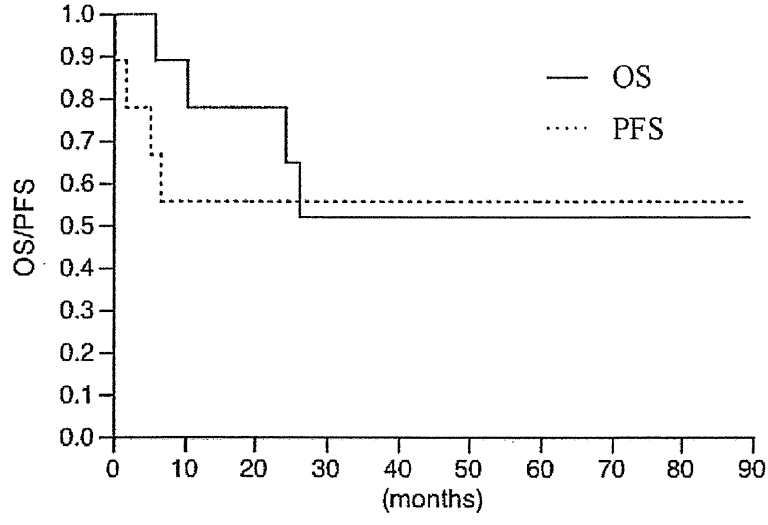

Fig. 1. Survival rates of all patients.
Overall survival rates and Progression free survival rates of all patients (n = 9), plotted by the Kaplan-Meier method.

a median follow-up duration of 47.4 months (range from 10.5 to 86.4), four out of five stage IB patients were alive without recurrence at the time of analysis. The response rate of CCRT as primary therapy was 75% (CR: 1, PR: 2, PD: 1). Remarkably, one patient with stage IVB disease was alive without recurrence at 89.5 months.

The median OS periods for those who survived and died during the evaluation period were 59.6 and 17.5 months, respectively. The OS and PFS rates for all patients at five years were 52% and 56%, respectively (Fig. 1). The patients with early stage disease had an 80% three-year OS compared to 25% for patients with advanced stage disease. There was no significant difference between the early stage group and the advanced stage group (Fig. 2A, B). Relapse sites included the vaginal cuff (n = 1), bone marrow (n = 1), lung (n = 2), bone (n = 1), and lymph node (n = 1). All patients with relapse were dead within three years of the first treatment.

Discussion

SCCC is a rare and carries a poor prognosis, primarily due to its propensity for early hematogenous and lymphatic spread. Many authors have recommended adjuvant chemotherapy due to the aggressive behavior of this tumor (Chang et al. 1998; Boruta et al. 2001); however, it is difficult to perform a large scale randomized controlled study given the rarity of the condition. The Gynecologic Oncology Group attempted to study small cell cervical carcinoma in protocol 66 between 1982 and 1986, but failed to recruit sufficient numbers of patients. Consequently, treatments for SCCC have been largely extrapolated from the experience with SCLC. SCLC is highly responsive to multiple chemotherapeutic drugs, and chemotherapy dramatically prolongs survival compared to best supportive care (Agra et al. 2003). In multiple randomized trials, the PE regimen appears to be at least as effective as older regimens such as vincristine, doxorubicin, and cyclophosphamide (VAC) and has less toxicity for SCLC (Fukuoka et al. 1991; Sundstrom et al.

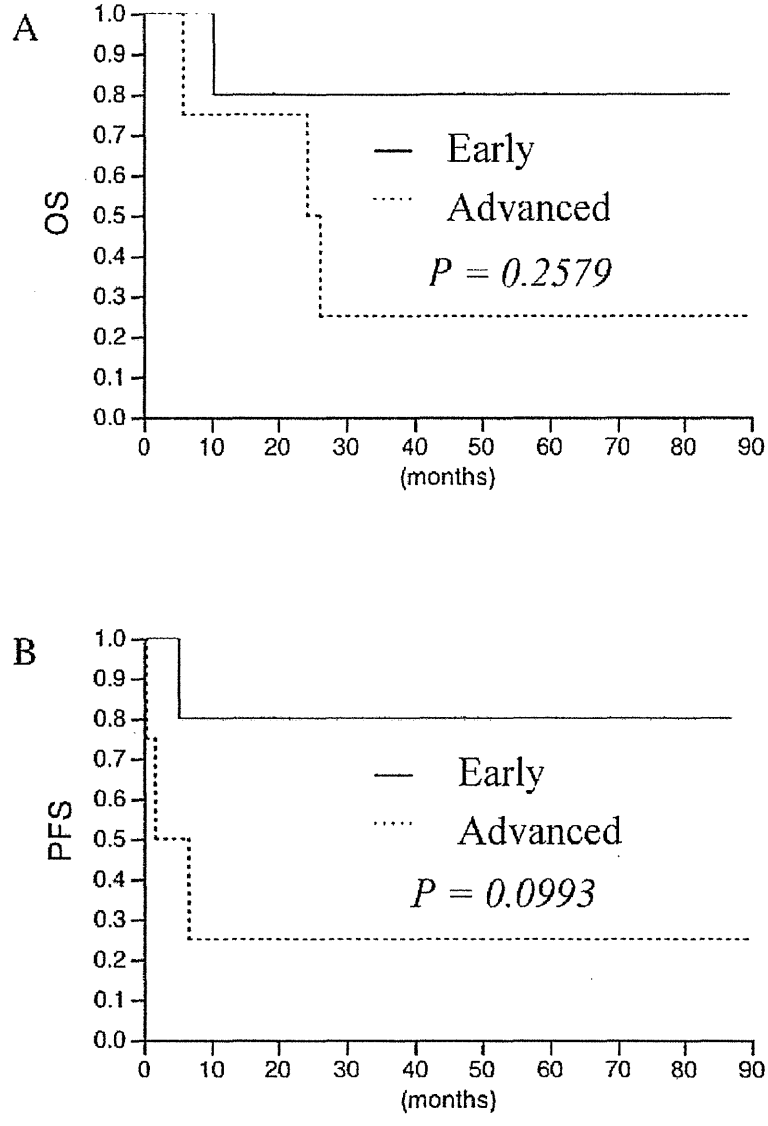

Fig. 2. Comparison between early and advanced stage.
(A) Overall survival rates. (B) Progression free survival rates of early stage (n = 5) and advanced stage (n = 4), plotted by the Kaplan-Meier method.

2002). Recently, as with SCLC, early stage patients with SCCC who received post-operative PE regimen with or without radiation experienced an 83% three-year recurrence-free survival, compared to 0% for those who did not receive adjuvant chemotherapy (Zivanovic et al. 2009). In addition to chemotherapy, there is a significant role for radiation therapy in the treatment of limited stage SCLC (Gaspar et al. 2005). In general, for patients with limited stage-SCLC, the PE regimen is used in conjunction with thoracic radiation because the PE regimen has little mucosal toxicity and modest hematologic toxicity.

To establish the appropriate therapy for SCCC, both the standard treatment for uterine cervical cancer, as well as the similarities in biologic behavior between SCLC and SCCC should be considered. In 1999, NCI issued a clinical alert that CCRT should be considered the standard of care over radiotherapy alone for women with cervical cancer, and concurrent cisplatin (40 mg/m2 weekly for five weeks) with external beam RT (50 Gy) is now widely used in both the primary and adjuvant settings. According to the clinical guidelines for cervical cancer treatment in Japan, postoperative CCRT using weekly cisplatin is recommended for patients at high risk of recurrence (Nagase et al. 2010). However, there is a room for discussion whether this setting is suitable for histological subtypes other than SCC. The Society of Gynecologic Oncology (SGO) also proposed that combination chemotherapy with radiation should be considered for non-surgical candidates with neuroendocrine carcinoma of the uterine cervix, with emphasis on individualized treatment (Gardner et al. 2011). Despite the lack of prospective data,