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# Clinical value of routine serum squamous cell carcinoma antigen in follow-up of patients with locally advanced cervical cancer treated with radiation or chemoradiation

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**Objective**
The objective of this study was to evaluate the clinical benefits of routine squamous cell carcinoma antigen (SCC-Ag) monitoring of patients with locally advanced cervical squamous cell carcinoma treated with radiation or chemoradiation.

**Methods**
A total of 53 patients with recurrent cervical squamous cell carcinoma treated with radiotherapy or chemoradiation were enrolled in this study. A retrospective review of medical records was conducted. The role of routine monitoring of serum SCC-Ag was evaluated in terms of cost effectiveness and effect on survival after diagnosis of recurrence.

**Results**
Serum SCC-Ag abnormality (≥2.5 ng/mL) was observed in 62.3% of patients when recurrent disease was diagnosed. The first indicator of relapse was abnormal serum SCC-Ag level in 21 patients (39.6%), 10 of whom had asymptomatic recurrent disease amenable to salvage therapy. Adding SCC-Ag measurement to the basic follow up protocol improved the sensitivity for detecting recurrence (The sensitivity of the basic protocol vs. addition of SCC-Ag: 49.1% vs. 88.7%, $P<0.001$). Twenty-three patients who were candidates for salvage therapy with curative intent showed better survival compared with those who were not candidates for therapy (5-year survival: 36.6% vs. 0%, $P=0.012$).

**Conclusion**
Surveillance with routine serum SCC-Ag monitoring can better detect asymptomatic recurrent disease that is potentially amenable to salvage therapy with curative intent. Early diagnosis of recurrent disease that can be treated with salvage therapy may lead to better survival.

**Keywords:** Chemoradiotherapy; Squamous cell carcinoma-related antigen; Surveillance; Uterine cervical neoplasms

## Introduction

Cervical cancer is a malignant disease that develops in the cervix; with increasing use of the Pap smear for screening, the incidence and mortality rate have decreased significantly. Moreover, with the development of vaccines after discovering the causative agent to be a high-risk human papillomavirus, cervical cancer is now the first preventable cancer. However, after breast cancer, cervical cancer remains the second most common cancer among women worldwide. Surgical treatment is used when the cancer is detected at an early stage, and concurrent chemoradiotherapy (chemoradiation) is used

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as the standard therapy for locally advanced cancer [1,2].

After completion of primary treatment, patients are followed for the possibility of recurrence using methods recommended by the Society of Gynecologic Oncology (SGO) and National Comprehensive Cancer Network (NCCN) [3]. To detect recurrence, histories are reviewed and physical examinations are conducted at every visit, and an annual Pap smear is recommended. A radiologic test or a blood test is recommended when there are symptoms of recurrence, abnormal physical findings, or abnormal Pap smear results.

Although a serum tumor marker test is not included in the routine post-treatment surveillance recommended by the SGO, squamous cell carcinoma antigen (SCC-Ag) is commonly used as a tumor marker for squamous cell cervical carcinoma, and carcinoembryonic antigen for adenocarcinoma [2]. SCC-Ag is a 45-kDa glycoprotein, with two types: SCC-1 and SCC-2 [4]. Increased serum SCC-Ag levels are commonly observed in squamous cell carcinoma of the esophagus, lungs, head and neck, anus, and cervix, but levels may also increase in benign diseases such as skin disorders, pelvic inflammatory disease, cystitis, and renal failure [4,5]. The serum SCC-Ag level at the time of diagnosis is correlated with the tumor stage, size, depth of invasion, parametrial invasion, and lymph node metastasis [4,6,7]. Moreover, the serum SCC-Ag level is associated with the patient's response to treatment [8-10].

Increase in serum SCC-Ag levels at recurrence above identified thresholds was observed in 46% to 92% of patients; this increase occurred at an average of 2 to 8 months prior to clinical diagnosis of the recurrence. The increase in SCC-Ag levels is the first evidence of recurrence in 15% of patients [11,12]. However, using the SCC-Ag test during regular checkups is not recommended for asymptomatic patients [2,3,13], because, thus far, the survival benefit of post-recurrence salvage therapy, except surgery for central pelvic recurrence, is still uncertain [14]. For the same reasons, radiologic tests are not recommended at every visit for asymptomatic patients not suspected to have a recurrence [2,3,13].

The treatment method for recurrent cervical cancer depends on the type of primary treatment and the location of recurrence. When recurrence occurs in the pelvis after surgery as the primary treatment, radiation or concurrent chemoradiotherapy can be used as salvage therapy [15]. When radiation or concurrent chemoradiotherapy was used as the primary treatment, few patients are candidates for salvage therapy with curative intent. Patients with central pelvic recurrence or isolated para-aortic lymph node recurrence without previous radiation treatment can be treated with surgery (radical hysterectomy or pelvic exenteration) and with chemoradiation, respectively [16-22]. Furthermore, because several studies showed a survival benefit of surgical resection for pulmonary metastasis [23,24], patients with distant metastasis that can be completely resected also might be candidates for salvage therapy. These data suggest that current post-treatment surveillance focused on detecting central pelvic recurrence needs to be re-evaluated.

The objective of this study was to evaluate the clinical benefits of routine SCC-Ag monitoring of patients with locally advanced cervical squamous cell carcinoma treated with radiation or chemoradiation. The clinical benefits were evaluated based on two goals: first, the improvement of sensitivity for recurrent disease detection by the addition of serum SCC-Ag testing to the basic surveillance protocol recommended by SGO, and second, the influence of salvage therapy on post-recurrence survival to assess value of the effort to detect asymptomatic recurrence.

## Materials and methods

### 1. Patients

We studied patients with relapse among those diagnosed with locally advanced cervical squamous cell carcinoma who underwent radiation or concurrent chemoradiotherapy between January 1, 2000 and December 31, 2014 at the Department of Gynecology and Radiation Oncology at the Daegu Catholic University Medical Center. Adenocarcinoma patients and patients who had never had their serum SCC-Ag tested during follow-up were excluded. Furthermore, patients were also excluded if they had received radiation and concurrent chemoradiotherapy as adjuvant therapy after radical hysterectomy as the primary treatment.

### 2. Methods

The patients' medical records and test results for the diagnosis of recurrence were retrospectively examined. Patients underwent regular checkups after primary treatment. The patient's history and physical examination, Pap smear, chest radiography, and serum SCC-Ag test were evaluated every 2 to 3 months for the first 2 years, once every 4 to 6 months for the

next 3 years, and annually after 5 years. A radiologic test was conducted every 6 to 12 months even when there were no symptoms present, and all necessary examinations, including biopsy, and radiologic tests, such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)-CT were conducted when there were symptoms of recurrence or abnormal results from other tests.

A diagnosis of recurrence was defined as a recurrence confirmed by biopsy or a radiological test showing progression of a lesion. In addition, when lesions persisted for 3 months after primary treatment with radiation or concurrent chemoradiotherapy, it was considered persistent cervical cancer and diagnosed as a recurrence. Disease-free interval was defined as the period between the completion of primary treatment and the diagnosis of the recurrence.

Considering the location and number of recurrent lesions as well as the previous treatment, we categorized recurrent lesions amenable to salvage therapy with curative intent as follows: 1) central pelvic recurrence, 2) para-aortic lymph node recurrence that was not previously treated with radiation, and 3) distant metastatic lesions that could be completely resected.

Among patients who could receive salvage therapy for recurrent lesions, some did not receive aggressive therapy such as surgery, radiation, and concurrent chemoradiotherapy for various reasons, including refusal of treatment. In contrast, there were patients with distant metastasis, such as pulmonary metastasis and lymph node metastasis, who received aggressive therapy, including surgery or radiation. Therefore, we categorized the patients into those who received aggressive therapy, such as surgery, radiation, or concurrent chemoradiotherapy, and those who only received chemotherapy or did not receive any treatment, and we compared the difference in survival.

In addition, post-treatment surveillance protocols were divided as follows to evaluate the improvement of sensitivity for detecting recurrent lesions by adding serum SCC-Ag testing: 1) basic protocol: a basic screening method that included taking the history, performing a physical examination, and obtaining a Pap smear; and 2) addition of serum SCC-Ag: a method that includes testing the serum SCC-Ag in addition to the basic screening method.

In searching for evidence of recurrence by evaluating symptoms, physical examination findings, Pap smear results, serum SCC-Ag values, chest radiography findings, and CT/MRI/PET-CT findings, the earliest diagnostic evidence that suggested recurrence or abnormal results was defined as the 'first indicator of relapse'. Symptoms suggesting recurrence were vaginal bleeding, vaginal bloody discharge, lower abdominal pain, pelvic pain, sciatic pain, weight loss, and general weakness. Examples of signs suggesting recurrence were abnormal pelvic findings (a mass or ulceration), and palpable enlarged lymph nodes (inguinal, supraclavicular, or axillary lymph nodes).

### 3. Serum squamous cell carcinoma antigen measurement and cutoff value

Serum SCC-Ag was measured using an immunoradiometric assay (Abbott Diagnostics, Chicago, IL, USA). Many previous studies have used a serum SCC-Ag range of 1.5 to 3 ng/mL as the upper normal limit [4,9,14,25]. Therefore, values ≥2.5 ng/mL were considered abnormal in this study [9].

### 4. Statistical analysis methods

The McNemar test was used to analyze the difference between the sensitivity of the basic protocol and that of the Addition of serum SCC-Ag protocol. The difference in frequency between the two comparison groups was analyzed with a chi-square test. Differences in the survival rate based on each clinical variable were analyzed using the Kaplan-Meier method and the log rank test. Differences with a *P*-value <0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS ver. 19 (IBM Co., Armonk, NY, USA).

## Results

Of the 355 patients who were treated with radiation or concurrent radiotherapy for locally advanced cervical squamous cell carcinoma, 53 were diagnosed with recurrence. The characteristics of the patients at the time of first diagnosis and at the time of recurrence are summarized in Table 1. A total of 23 patients showed recurrence in regions amenable to salvage therapy, such as central pelvic recurrence or para-aortic lymph node recurrence not treated previously with radiotherapy. Twenty-six patients received aggressive therapy, such as surgery, radiation, and concurrent chemoradiotherapy, after the recurrence, and the remaining patients received chemotherapy or only conservative management. The serum SCC-Ag level at the time of diagnosis of recurrence was ≥2.5 ng/mL in 33

**Table 1.** Characteristics of enrolled patients

| Characteristics | | Value |
|---|---|---|
| Age (yr) | | 53.0±12.9 |
| Initial stage | IB | 8 (15.0) |
| | IIA | 2 (3.8) |
| | IIB | 22 (41.5) |
| | IIIB | 14 (26.4) |
| | IVA | 7 (13.2) |
| Initial serum SCC-Ag level (ng/mL) | | 21.0±22.3 |
| Disease free interval (mo) | <12 | 27 (50.9) |
| | ≥12 | 26 (49.1) |
| Initial treatment modality | Chemoradiation | 48 (90.6) |
| | Radiotherapy | 5 (9.4) |
| Radiation field for primary therapy | Pelvic radiation | 44 (83.0) |
| | Extended field | 8 (15.1) |
| Site of recurrence | Central pelvic | 7 (13.2) |
| | Pelvic side wall | 9 (17) |
| | Isolated para-aortic lymph node | 14 (26.4) |
| | Distant metastasis or combined metastasis | 23 (43.4) |
| Serum SCC-Ag level at recurrence (ng/mL) | <2.5 | 20 (37.7) |
| | ≥2.5 | 33 (62.3) |
| Treatment modality for recurrent disease | Supportive care | 11 (20.8) |
| | Chemotherapy | 16 (30.2) |
| | Surgery | 7 (13.2) |
| | Radiotherapy | 8 (15.1) |
| | Chemoradiation | 11 (20.8) |

Values are presented as mean±standard deviation or number (%).
SCC-Ag, squamous cell carcinoma antigen.

**Table 2.** Diagnostic modalities showing abnormal findings at the diagnosis of recurrence

| Diagnostic modalities | No. (%)[a] |
|---|---|
| Symptoms | 21 (36.9) |
| Physical examination | 5 (9.4) |
| Pap smear | 3 (5.7) |
| SCC-Ag | 33 (62.3) |
| Chest X-ray | 1 (1.9) |
| Computed tomography | 41 (77.4) |
| Magnetic resonance imaging | 7 (13.2) |
| Positron emission tomography | 20 (37.7) |

SCC-Ag, squamous cell carcinoma antigen.
[a]The total sum of percentages is not 100% because multiple abnormalities were founded in some patients.

patients (62.3%) (Table 1).

The symptoms, signs, blood test results, and radiologic test results at the time of diagnosis of recurrence are summarized in Table 2. There were 39.6% of the patients who showed symptoms indicating recurrence, 9.4% who showed abnormal findings during physical examination, and 5.7% who showed abnormal Pap smear results (Table 2). Increased serum SCC-Ag levels at the time of diagnosis of recurrence was more common in patients with high serum SCC-Ag levels at initial diagnosis; 27.3% of the patients who had normal SCC-Ag at initial diagnosis showed an elevated serum SCC-Ag level, while 73% of patients who had high serum SCC-Ag levels at initial diagnosis showed an elevated serum SCC-Ag level ($P$=0.011).

The basic protocol (as recommended by the SGO) included

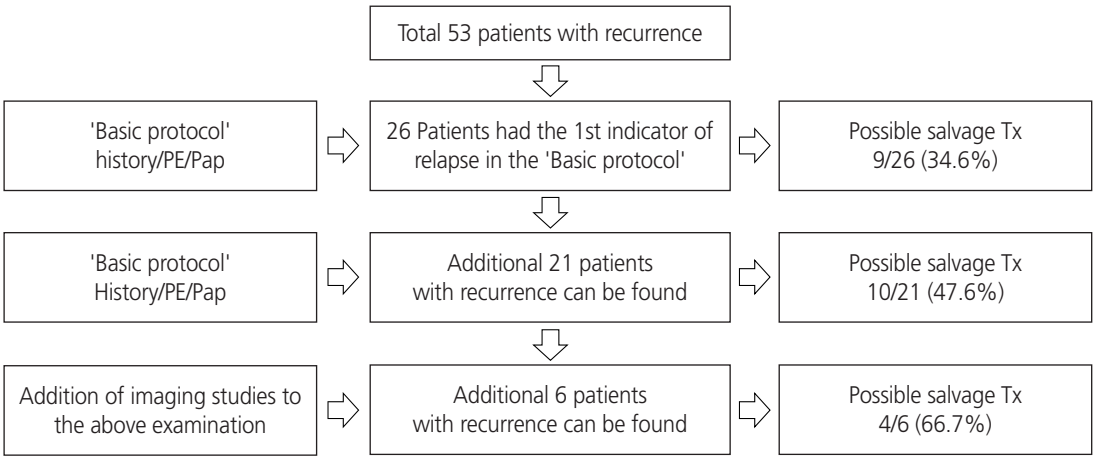


**Fig. 1.** The number of patients showing each first indicator of relapse according to post-treatment surveillance protocol and the proportion of patients who were candidates for salvage therapy. PE, physical examination; Pap, Papanicolaou smear; SCC-Ag, squamous cell carcinoma antigen; Tx, treatment.

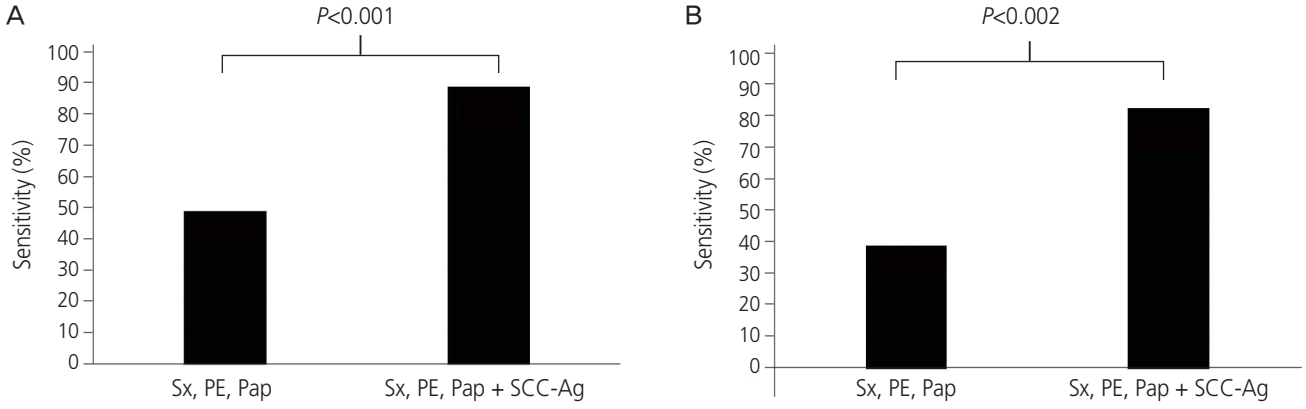


**Fig. 2.** (A) The comparison of the sensitivity in the ability to detect recurrence between the basic protocol and the addition of serum squamous cell carcinoma antigen (SCC-Ag) to basic protocol in all the patients with recurrence. Basic protocol: history-taking, physical examination, Pap smear. (B) The comparison of the sensitivity in the ability to detect recurrence between the basic protocol and the addition of serum SCC-Ag to basic protocol in patients with recurrence who were candidates for salvage therapy. Sx, symptom; PE, physical examination; Pap, Papanicolaou smear.

obtaining a history, performing a physical examination, and obtaining a Pap smear, while the addition of serum SCC-Ag method included serum SCC-Ag testing in addition to the basic protocol. A total of 26 patients had their first indicator of relapse detected by the basic protocol, and 9 (34.6%) were candidates for salvage therapy. With the addition of the serum SCC-Ag test to the basic protocol, an additional 21 asymptomatic patients with recurrence could be identified, and 10 (47.6%) were candidates for salvage therapy (Fig. 1). When the serum SCC-Ag test was added to the basic protocol, 88.7% of recurrences could be identified (the sensitivity of the basic protocol vs. addition of SCC-Ag: 49.1% vs. 88.7%, $P$<0.001) (Fig. 2A). Of the 23 patients who were candidates for salvage therapy, 19 (82.6%) showed abnormal findings by the addition of serum SCC-Ag method (the sensitivity of the basic protocol vs. addition of SCC-Ag: 39.1% vs. 82.6%, $P$=0.002) (Fig. 2B).

The 23 patients with recurrence who were amenable to salvage therapy had better outcomes than the patients who could not be salvaged (5-year overall survival: 36.6% vs. 0%, $P$=0.012) (Fig. 3A). Moreover, compared with patients who did receive chemotherapy or conservative management, those who received aggressive therapy such as surgery, radiation and concurrent chemoradiotherapy has a better outcome (5-

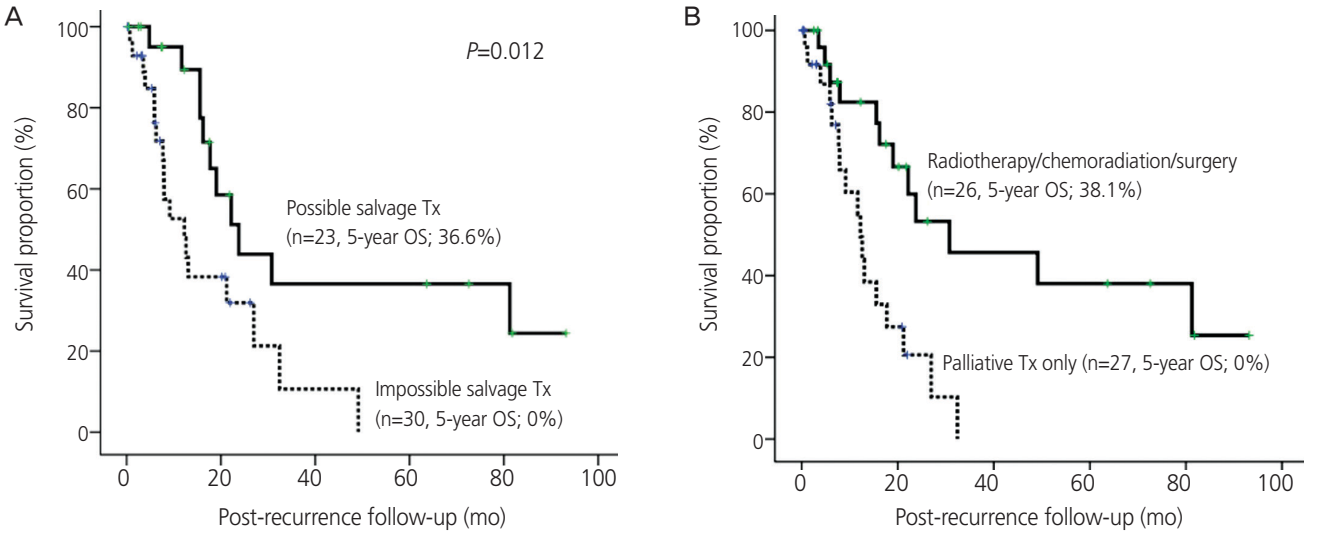


**Fig. 3.** (A) The comparison of survival outcomes between the patients who were candidates for salvage therapy and those who were not. (B) The comparison of survival outcomes between the patients who received aggressive therapy (radiotherapy/chemoradiation/surgery) and those who received palliative therapy. Tx, treatment; OS, overall survival.

**Table 3.** Eight patients surviving >30 months after the diagnosis of recurrence

| Recurrent site | Therapeutic methods for recurrent disease | Survival time after recurrence (mo) | Last follow-up status |
|---|---|---|---|
| Cervix | Surgery | 30.7 | Death from disease |
| Cervix and pelvic side wall | Chemotherapy | 32.4 | Death from disease |
| Lung | Surgery & chemotherapy | 49.2 | Death from disease |
| Cervix | Radiation | 63.7 | Alive without disease |
| Cervix | Chemoradiation | 72.6 | Alive without disease |
| Cervix | Surgery | 81.3 | Death from disease |
| Vagina | Surgery | 81.8 | Alive without disease |
| Para-aortic lymph node | Chemoradiation | 93.2 | Alive without disease |

year overall survival: 38.1% vs. 0%, *P*=0.001) (Fig. 3B).

Eight patients survived for >30 months after recurrence was diagnosed: six had central pelvic recurrence (in the cervix and vagina); one had para-aortic lymph node metastasis, was treated with concurrent chemoradiotherapy, surviving for 93.2 months with no evidence of disease; and one had pulmonary metastasis and underwent surgery three times with postoperative adjuvant chemotherapy, surviving 49.2 months after recurrence before succumbing to disease (Table 3).

## Discussion

At the time cervical cancer recurrence is diagnosed, 46% to 95% of patients show symptoms such as abdominal pain, pelvic pain, leg pain, leg swelling, vaginal bleeding, vaginal discharge, urinary tract symptoms, coughing, or weight loss [3,13]. In this study, 39.6% of patients complained of symptoms at the time of recurrence; lumbar pain, abdominal pain, and leg pain were the most common symptoms. When these symptoms were the first indicators of relapse, few cases were curable with salvage therapy. Therefore, regular checkups are required after treatment, and pelvic examination is the most important follow-up examination, because isolated central pelvic recurrence can be salvaged with radical hysterectomy or pelvic exenteration, depending on tumor size. This study also showed that most patients with long-term survival after recurrence had isolated central pelvic recurrence. Abnormal findings during physical examinations can be observed in 29% to 75% of patients with recurrent cervical cancer after primary

treatment [3]. In this study, abnormal physical examination findings were observed only in 9.4% of all relapsed patients. The smaller proportion of patients with symptoms or abnormal physical examination findings in this study compared with that reported in other studies can be explained because additional asymptomatic recurrences were found via routine serum SCC-Ag testing and periodic imaging studies.

The Pap smear has low sensitivity for diagnosing recurrence. Moreover, interpreting the test is even more difficult considering the changes in cells induced by radiation during radiotherapy [2,13]. For this reason, the SGO and NCCN recommend a regular Pap smear annually, and some researchers exclude the Pap smear from regular checkups [3,13]. Abnormal Pap smear findings were observed only in 5.7% of patients in this study. Although previous studies reported that chest radiographs found abnormal findings in 20% to 47% of relapsed patients [3,13], abnormal findings were observed in only 1.9% of patients in this study. Therefore, chest radiography did not play a significant role in diagnosing recurrence, especially for asymptomatic patients. Furthermore, even when pulmonary or pleural metastasis is diagnosed on chest radiography, it is difficult for these patients to receive salvage therapy with curative intent.

The SGO and NCCN recommend periodic history taking, a physical examination, and a Pap smear as post-treatment surveillance. For patients with a high risk of disease recurrence, e.g., those who required concurrent chemoradiotherapy or radiotherapy as primary treatment for advanced diseases or who required postoperative adjuvant therapy, they recommend history and physical examination every 3 months for the first 2 years after treatment, and then every 6 months for the next 3 years. For patients at low risk of disease recurrence, e.g., who were diagnosed at an early stage and treated with surgery alone, history taking and physical examination are recommended every 6 months for the first 2 years, and annually thereafter [3]. The Pap smear is recommended annually. They recommend a blood test or a radiological test as a follow-up method only when patients are suspected to have recurrence based on symptoms, physical examination findings or abnormal Pap smear results.

These guidelines were established because few patients can be cured by salvage therapy with curative intent. The survival benefit of surgical salvage therapy for central pelvic recurrence after primary radiotherapy is well established [16,19]. Thus, diagnosis based on physical examination and Pap smear is the most important method for detecting pelvic recurrence during follow-up.

If only patients with central pelvic recurrence after primary radiotherapy are candidates for salvage therapy, efforts to detect other types of recurrence do not have clinical significance. However, patients with isolated para-aortic lymph node recurrence without previous radiation exposure also may be candidates for salvage therapy [18,20-22]. Furthermore, because pulmonary metastasis reflects distant hematogenous metastasis, pulmonary metastatic lesions have not been treated aggressively such as by surgical resection. However, surgical resection of pulmonary metastatic lesions can prolong survival, especially when fewer than three lesions are present [23,24]. Thus, the role for aggressive salvage therapy is expanding.

Many research studies have focused on the effectiveness of including serum SCC-Ag testing during post-treatment follow-up. Forni et al. [26] reported that simplified follow-up using only pelvic examination and serum SCC-Ag testing has a 2.2% possibility of failing to diagnose recurrences, compared with performing all tests including radiologic studies, and its cost was only 1/12 of the cost of performing all recommended studies. Micke et al. [8] also reported that serum SCC-Ag testing was helpful in early detection of recurrence. However, few studies have evaluated whether early detection of recurrent lesions results in a better prognosis, and there are no prospective comparative studies. Ogino et al. [21] conducted a study including 99 patients with recurrent cervical cancer, and demonstrated that the addition of serum SCC-Ag testing during regular checkups was helpful in rapid diagnosis of isolated para-aortic lymph node recurrence. In addition, as radiotherapy results in a better prognosis for recurrence in the para-aortic lymph nodes than for recurrence in other regions, serum SCC-Ag testing can be helpful in improving survival after recurrence. In a study of 167 patients with recurrent cervical cancer, Shimura et al. [27] showed that, when the serum SCC-Ag level at the time of recurrence was <14 ng/mL, patients who received aggressive treatment such as radiation therapy or surgery showed better outcomes than those who did not, whereas when the serum SCC-Ag level was >14 ng/mL, there was no significant difference in outcome based on aggressive therapy. The current study demonstrated that recurrence that can be treated with salvage therapy had a better outcome than recurrence that was not amenable to salvage therapy, and patients that received aggressive treatment including surgery, radiation, or concurrent chemoradiotherapy also had a

better outcome than those that received only chemotherapy or conservative management. These findings suggest that efforts toward early detection of recurrence after radiotherapy or chemoradiation can affect prognosis.

If aggressive salvage therapy after recurrence can contribute to improved survival, the next question will be, what is the most effective method for early diagnosis of recurrent disease? Of all radiologic tests, $^{18}$FDG PET-CT has a sensitivity, specificity, and accuracy for detecting recurrence of 92%, 92.6%, and 92.3%, respectively, which is helpful in detecting asymptomatic recurrent lesions. However, using $^{18}$FDG PET-CT at every visit for asymptomatic patients is not cost-effective, and has the disadvantage of radiation exposure during testing [13,28-31]. Rather than including radiologic testing in regular checkups for asymptomatic patients, inclusion of serum SCC-Ag testing in regular checkups is more cost-effective [26]. This study showed similar findings that when radiological tests such as chest X-ray, CT, MRI, or PET-CT were used in asymptomatic patients who showed normal results on physical examinations, Pap smear, and serum SCC-Ag test, the probability of incidentally diagnosing recurrence was 11.3%.

To utilize serum SCC-Ag testing at follow-up, it was challenging to determine the ideal threshold value for diagnosing recurrence, as previous studies had used values of 1.5 to 3 ng/mL for the upper normal limit of serum SCC-Ag [4,9,14,25]. Lowering the threshold value increases the sensitivity but decreases specificity, and vice versa. Results from this study were obtained considering serum SCC-Ag levels ≥2.5 ng/mL to be abnormal [9].

With the exception of central pelvic recurrence after radiation/chemoradiation and pelvic recurrence after surgical treatment, the survival benefit of salvage therapy for recurrent cervical cancer is unclear. However, since a better outcome was observed in patients who received aggressive salvage therapy and treatment than those receiving conservative management in our present study, it is important to try to diagnose recurrent lesions early. Of the tests available, the serum SCC-Ag test has a higher probability of detecting recurrent lesions, compared with history taking, physical examination, and a Pap smear alone, and it is superior to radiologic testing in terms of cost-effectiveness. Further results should be obtained by conducting prospective studies that directly compare the outcome between patients when the serum SCC-Ag test is included and those for whom the serum SCC-Ag test is not included in follow-up after treatment for cervical cancer. The limitations of this study included its retrospective study design with a limited number of patients, and that there was no direct comparison between the basic surveillance protocol and the addition of serum SCC-Ag testing to the basic protocol.

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

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