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Original Article

Practice patterns of adjuvant therapy for intermediate/high recurrence risk cervical cancer patients in Japan

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ABSTRACT

Objective: Although radiation therapy (RT) and concurrent chemoradiotherapy (CCRT) are the global standards for adjuvant therapy treatment in cervical cancer, many Japanese institutions choose chemotherapy (CT) because of the low frequency of irreversible adverse events. In this study, we aimed to clarify the trends of adjuvant therapy for intermediate/high-risk cervical cancer after radical surgery in Japan.
Methods: A questionnaire survey was conducted by the Japanese Gynecologic Oncology Group to 186 authorized institutions active in the treatment of gynecologic cancer.
Results: Responses were obtained from 129 facilities. Adjuvant RT/CCRT and intensity-modulated RT were performed in 98 (76%) and 23 (18%) institutions, respectively. On the other hand, CT was chosen as an alternative in 93 institutions (72%). The most common regimen of CT, which was used in 66 institutions (51%), was a combination of cisplatin/carboplatin with paclitaxel. CT was considered an appropriate alternative option to RT/CCRT in patients with risk factors such as bulky tumors, lymph node metastasis, lymphovascular invasion, parametrial invasion, and stromal invasion. The risk of severe adverse events was considered to be lower for CT than for RT/CCRT in 109 institutions (84%).
Conclusion: This survey revealed a variety of policies regarding adjuvant therapy among institutions. A clinical study to assess the efficacy or non-inferiority of adjuvant CT is warranted.

Keywords: Adjuvant Therapy; Drug Therapy; Radiation; Uterine Cervical Neoplasms

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

INTRODUCTION

Cervical cancer is the third most common cause of death among gynecologic cancers [1]. Women with stage IA2 to IIA lesions require radical hysterectomy with bilateral pelvic lymph-node dissection, radiation therapy (RT), or concurrent chemoradiotherapy (CCRT) [2,3]. In Japan, more than 80% of institutions choose radical hysterectomy as the primary therapy for patients with stage IB1 and IIA1 tumors [4]. After the surgical procedure, the recurrence risk is evaluated by pathological criteria such as lymph node metastasis, lymphovascular space invasion, depth invasion, parametrial invasion, nonsquamous histology, and positive surgical margins [5-8]. Subsequently, adjuvant therapy is considered for patients with an intermediate/high risk of recurrence.

RT decreases the incidence of local recurrence when used as an adjuvant therapy [9,10]; however, there is little or no effect on overall survival [11,12]. On the other hand, CCRT improves progression-free and overall survival for high-risk and early-stage patients who undergo radical hysterectomy and pelvic lymphadenectomy [13]. The National Comprehensive Cancer Network (NCCN) recommends pelvic RT/CCRT for high-risk patients [2]. The Japan Society of Gynecologic Oncology treatment guidelines for cervical cancer also follow the NCCN policy with minor modifications [14]. However, 37% to 48% of recurrences in cervical cancer occur in the extra-pelvic area, and their prognosis is extremely poor [15,16]. In addition, patients who undergo RT may still experience late adverse events and toxicity because of the anatomic locations such as the bladder, bowel, vagina, and ovary [17]. In terms of the quality of life, RT has a disadvantage about sexual function in young women with cervical cancer [18]. Since complications exist over a long time and the mean age at diagnosis of cervical cancer is 48 years, many patients and physicians hesitate to choose RT/CCRT [19,20]. Although some institutions adopt an approach using intensity-modulated radiation therapy (IMRT) to reduce the adverse events, a longer follow-up is required to evaluate the benefit of this treatment [21].

Our previous study showed that many institutions in Japan use chemotherapy (CT) as an adjuvant therapy in patients with intermediate and high risk of recurrence [22]. However, to the best of our knowledge, no clinical study has been conducted to evaluate the efficacy or inferiority of CT as an adjuvant therapy for cervical cancer. In this study, we first aimed to clarify the current trends for adjuvant therapy in different institutions, then evaluated the need for a prospective study to assess CT as an adjuvant therapy for postoperative cervical cancer.

MATERIALS AND METHODS

A questionnaire was designed by a gynecological oncology clinical fellow who attended an educational seminar conducted by the Japanese Gynecologic Oncology Group (JGOG) in August 2013. The details of the questionnaire are listed in **Appendix**. Briefly, the questionnaire included the following questions:

(1) What kind of therapy is routinely selected as an adjuvant therapy for intermediate/high risk postoperative cervical cancer?
(2) What kind of regimen is used for adjuvant CT?
(3) What kind of chemotherapeutic agents are used for CCRT?

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(4) Does your institute perform IMRT?
(5) What do you select as a most appropriate adjuvant therapy for patients with risk factors such as bulky tumor, lymph node metastasis, lymphovascular invasion, parametrial invasion, stromal invasion, and vaginal stump invasion?
(6) Will you conduct or support a clinical study to evaluate appropriate adjuvant therapies for cervical cancer?

In August 2014, we mailed the questionnaire to all 186 JGOG member institutions. All the chosen hospitals treated gynecologic cancer and were authorized by the JGOG membership committee. Responses were accepted until December 2014.

RESULTS

1. Characteristics of responders' institutions

In total, 129 of the 199 JGOG member institutions replied to our questionnaire. The characteristics of responding institutions are shown in **Table 1**. Since JGOG membership extended only to institutions active in the treatment of gynecologic cancer, 69 (53%) and 14 (11%) of the 129 institutions were academic hospitals and cancer centers, respectively. Furthermore, 65 (50%) and 52 (40%) institutions had one and two (or more) gynecologic oncologists on the board of the Japanese Society of Gynecologic Oncology, respectively. The average number of radical hysterectomies performed annually was 5 to 15 and >15 in 64 (50%) and 48 (37%) institutions, respectively.

2. Practice patterns of adjuvant therapy for cervical cancer in Japan

First, current adjuvant therapy policies in each institution were analyzed. Our questionnaire allowed multiple answers because many institutions may have multiple therapeutic strategies based on the histological subtypes and/or number of risk factors. According to Japanese guidelines, CCRT/RT was performed in 98 institutions (76%) (**Fig. 1A**). On the other hand, 93 institutions (72%) also had the option to perform CT alone (**Fig. 1A**). IMRT was performed in 18% of institutions (**Fig. 1B**). The CCRT regimen was simple; 83% of institutions used cisplatin alone (**Fig. 1C**). However, multiple CT regimen were used; the most popular regimen, which was used in 46% of institutions, was a combination of carboplatin and paclitaxel, followed by irinotecan with nedaplatin (20%), and cisplatin with paclitaxel (17%) (**Fig. 1D**).

Table 1. Background of responding institutions

Variable	Institution (%)
Responder	129
Academic hospital	69 (53)
Cancer center	14 (11)
General hospital	46 (36)
Physicians with board of Japan Society of Gynecologic Oncology	
0	12 (10)
1	65 (50)
≥2	52 (40)
No. of radical hysterectomy per year	
<5	17 (13)
5–15	64 (50)
>15	48 (37)

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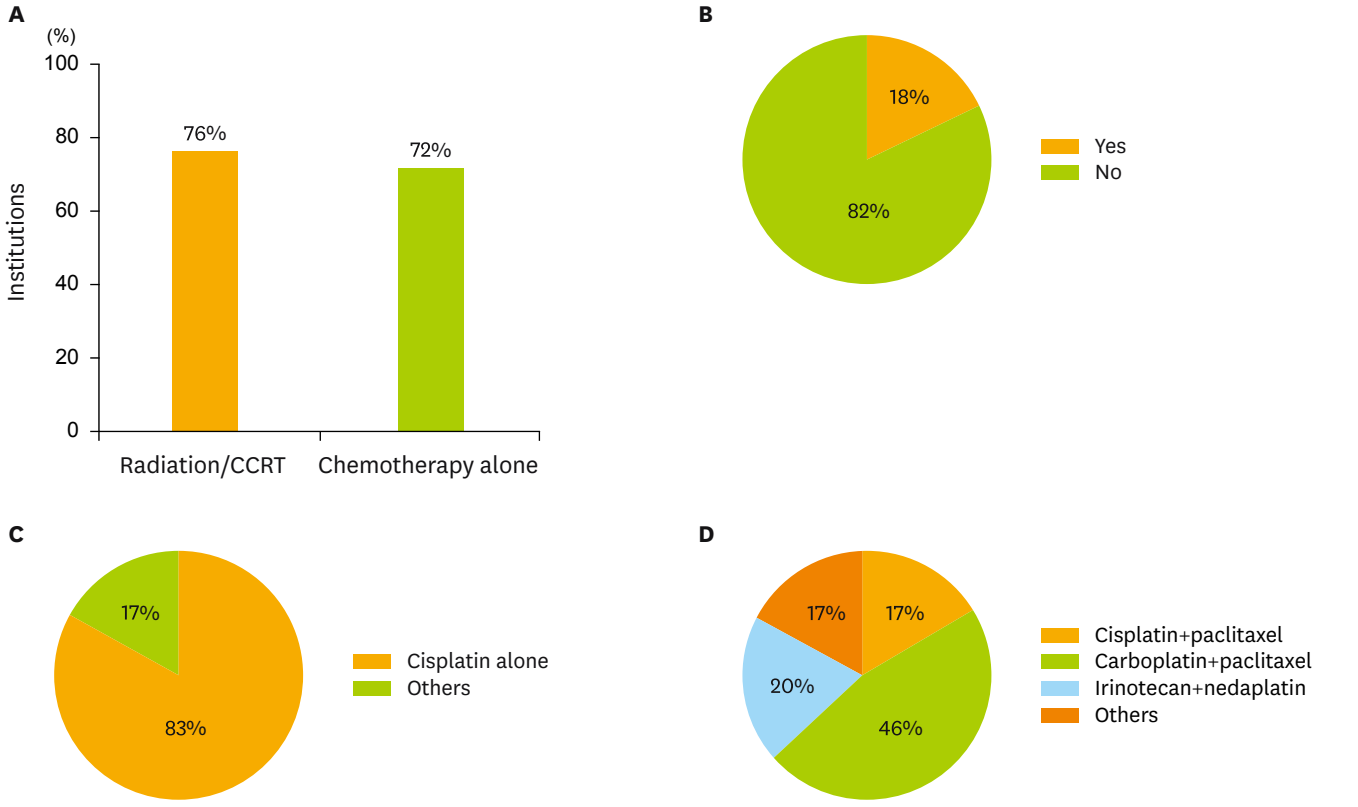

Fig. 1. Variety of adjuvant therapy policies for cervical cancer in Japan. The policy for adjuvant therapy was investigated in each institution (multiple answers allowed). (A) Therapeutic options considered for adjuvant therapy. (B) Percentage of institutions performing intensity-modulated radiation therapy. (C) Regimen for concurrent chemoradiotherapy (CCRT). (D) Regimen for adjuvant chemotherapy.

3. Risk assessment for clinicopathological factors

Next, we assessed risk assessment for clinicopathological factors which might be one of the reasons for the variety of adjuvant therapies. As shown in **Fig. 2**, RT was revealed to be the most appropriate adjuvant therapy for vaginal stump invasion cases, but not for other factors such as bulky tumor, lymph node metastasis, lymphovascular invasion parametrial invasion, and stromal invasion. CCRT was appropriate especially in cases of lymph node metastasis and parametrial invasion. Interestingly, CT ranked highly as an adjuvant therapy for all risk factors except vaginal stump invasion, and even for factors where observation was frequently chosen, for example, bulky tumors, lymphovascular invasion, and stromal invasion. These results indicate that the type of risk factor might affect the selection of adjuvant therapy.

4. Expectation of randomized controlled trial to evaluate the efficacy of CT as an adjuvant therapy in cervical cancer

Finally, we focused on how gynecologic oncologists evaluate the complications of each therapeutic option and the necessity of a trial to evaluate the efficacy or non-inferiority of CT as an adjuvant therapy in cervical cancer. The result showed that 85% of institutions evaluated CT as an adjuvant therapy with fewer incidences of severe complications (**Fig. 3A**). On the other hand, only 4% of institutions chose RT and 5% rated both CT and RT equally. Moreover, 87% of institutions were supportive of a clinical study to evaluate the efficacy or non-inferiority of CT as an adjuvant therapy in cervical cancer (**Fig. 3B**). Approximately 13% of institutions did not support a future clinical study because of the lack of radiation facilities or fewer cases for adjuvant therapy than expected (not shown in figure).

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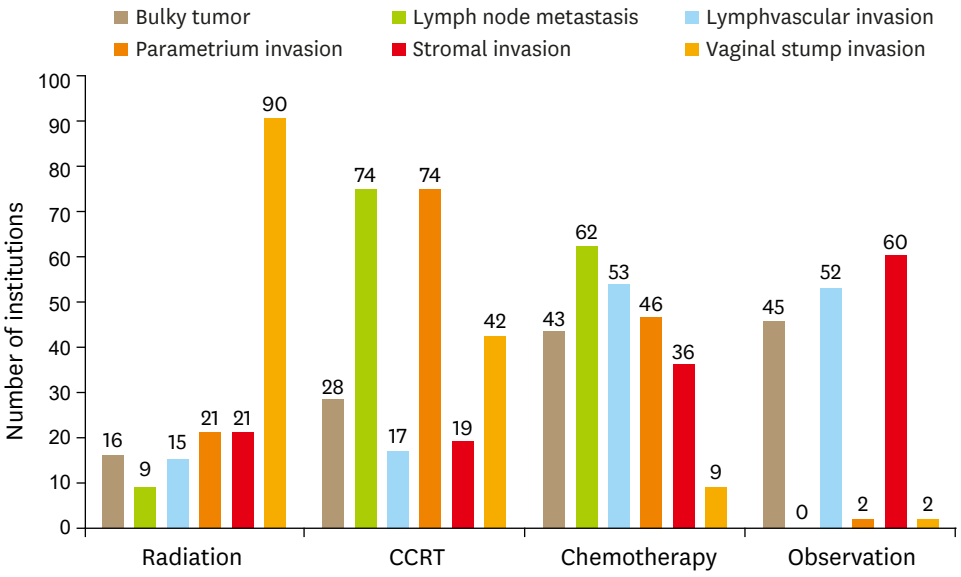

Fig. 2. Risk assessment for clinicopathological factors. Appropriate therapeutic options are chosen from among radiation, concurrent chemoradiotherapy (CCRT), chemotherapy, and observation (multiple answers allowed).

DISCUSSION

In this survey, we showed (1) the variety of adjuvant therapies for cervical cancer in Japan, (2) that the combination of risk factors might affect the selection of adjuvant therapy, and (3) that a clinical study is required to evaluate the efficacy or non-inferiority of CT as an adjuvant therapy in cervical cancer.

Previous retrospective studies had revealed the efficacy of CT as an adjuvant therapy for cervical cancer. A large-scale retrospective study in 2,268 patients comparing efficacy and adverse effects indicated no significant differences between CT and RT/CCRT in both the 5-year overall survival and disease-free survival [23]. Notably, the increased 5-year overall survival and disease-free survival rates of CT compared to RT were seen in patients with early-stage disease, clinical response, and younger age [23]. These results motivate gynecologic oncologists to use CT as an adjuvant therapy. Our survey also revealed that CT was a wise choice for adjuvant therapy in Japan.

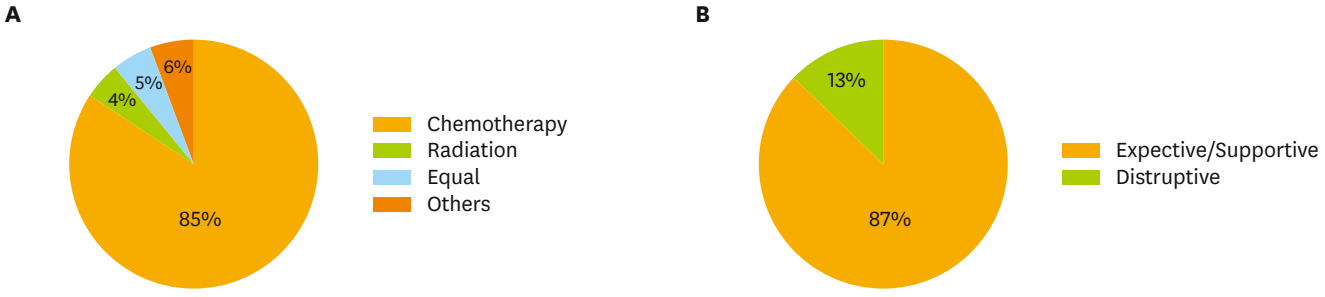

Fig. 3. Recognition of complications and requirement for a clinical study to assess adjuvant therapy. (A) Identification of the most reduced complication of adjuvant therapy. (B) The approach of your institution for clinical study to assess the efficacy or non-inferiority of chemotherapy as an adjuvant therapy.

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In our survey, the regimen for CCRT generally involved only cisplatin because previous meta-analysis including 4,580 randomized patients showed an improved overall survival (hazard ratio, 0.71; p<0.001) in CCRT compared to RT, and cisplatin was the most commonly used agent in the study [24]. However, the regimen for CT alone showed variety, for example, cisplatin with paclitaxel, carboplatin with paclitaxel, and irinotecan with nedaplatin. These regimens come from clinical studies of cervical cancer in Japan. Previously, a combination of paclitaxel and cisplatin was considered the standard CT for cervical cancer [25,26]. Recently, we reported the non-inferiority of the paclitaxel and carboplatin regimen compared to paclitaxel and cisplatin in patients with recurrent or metastatic cervical cancer [27].

Risk criteria should be considered before the selection of adjuvant therapy. Currently, recurrence risk is evaluated according to the number of risk factors found in the patient. However, our survey revealed that gynecologists assess the recurrence risk according to the kind of risk factors the patient has, and then choose the appropriate therapeutics. Radiation was supported by the majority of institutions for the adjuvant therapy of vaginal stump invasion. This is reasonable because RT such as brachytherapy can directly approach the tumor. In fact, the 10-year survival rate of non-palpable recurrence at the vaginal stump is reported to be more than 70% following brachytherapy alone [28]. On the other hand, postoperative CCRT was used for lymph node metastasis and parametrial invasion because previous randomized studies proved the efficacy of CCRT in these patients [13]. However, lymph node metastasis is considered as a significant risk factor for prognosis, even after CCRT/RT [29]. Notably, the 3-year survival rate of adjuvant CT was more than 78% and superior to that of radiotherapy (67%), even though 34% of patients had multiple lymph node metastases. In addition, CT has an equivalent therapeutic effect to RT with fewer postoperative complications [30,31]. Our results showed that many gynecologic oncologists in Japan also evaluate the superiority of CT according to the complication. These results support the need for evaluation of CT as an adjuvant therapy for cervical cancer. In fact, almost 90% of the institutions supported such a clinical study.

Our survey has several limitations. First, this study was performed for selected institutions. Since treatment for cervical cancer is generally performed in front-line medical centers and most of them belong to JGOG, we conducted this survey only in these institutions. Therefore, our result might not reflect the opinions in a small institution. Second, in this survey, we evaluated all institutions equally. Since the number of patients is different in each institution, some of the results might have to be evaluated considering the scale of the institution. In fact, some institutions in our survey have no radiation facility in their hospital. However, if the efficacy or non-inferiority of CT for adjuvant therapy is proven, these institutions can choose CT without any hesitation.

In conclusion, our study showed that a variety of adjuvant therapy policies for cervical cancer are currently in use in each institution. Clinical study to assess the efficacy or non-inferiority of adjuvant CT is required.

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Appendix. Questionnaire on the cervical cancer treatment policy of Japanese Gynecologic Oncology Group medical institutions

This questionnaire survey should be answered by the Head or responsible person of each institution.

1. Does your institution have criteria for performing adjuvant therapy for intermediate/high risk cervical cancer after surgery?
   1) According to the Japanese guidelines
   2) Almost the same as the Japanese guidelines
   3) Unique criteria, specific to the institution
   4) Other criteria

2. What according to you is the most appropriate adjuvant therapy for each of the recurrent risk factors listed below? (multiple answers allowed)
   1) Bulky tumor:
      (a) Observation, (b) Radiotherapy, (c) Chemotherapy, (d) Other

   2) Lymph node metastasis:
      (a) Observation, (b) Radiotherapy, (c) Chemotherapy, (d) Other

   3) Lymphovascular invasion:
      (a) Observation, (b) Radiotherapy, (c) Chemotherapy, (d) Other

   4) Parametrial invasion:
      (a) Observation, (b) Radiotherapy, (c) Chemotherapy, (d) Other

   5) Stromal invasion:
      (a) Observation, (b) Radiotherapy, (c) Chemotherapy, (d) Other

   6) Vaginal invasion:
      (a) Observation, (b) Radiotherapy, (c) Chemotherapy, (d) Other

3-1. What should be performed as an adjuvant therapy for intermediate/high risk postoperative cervical cancer? (multiple answers allowed)
   1) Chemotherapy
   2) Radiation
   3) Concurrent chemoradiotherapy (CCRT)
   4) Other

3-2. Why did you select this (these) therapy (therapies)?

4. What kind of regimen do you use for adjuvant chemotherapy?
   Agents:
   Dose:

5-1. What is total dose in Gy you use for adjuvant radiation therapy?

5-2. What kind of chemotherapeutic agents do you use for CCRT?
   Agents:
   Dose:

6. Does your institution perform Intensity-Modulated Radiation Therapy (IMRT)?
   1) Yes
   2) No, but we can perform IMRT.
   3) No. We can only perform conventional radiation therapy.
   4) No. We cannot perform radiation therapy.

7. Which therapy do you think has the fewest adverse events?
   1) Radiation
   2) Chemotherapy
   3) Equal
   4) Other

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