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## Two committees are obligated to secure the quality of JGOG researches

Kazunori Ochiai, M.D., Ph.D. President, JGOG

In this issue of the JGOG International, I would like to introduce two committees that are most important in the JGOG organization.

First comes the Ethics Committee. A clinical trial absolutely needs human subjects to whom an agent is administered and it cannot be performed unless subjects are fully explained about it and provide informed consent of their own free will. Protocol planners have, therefore, to describe in plain words what medical contributions are expected from it and how it is scientifically significant in the trial protocol as well as in the consent form. It is the duties of the Ethics Committee to objectively and fairly decide if clinical studies or trials are in accordance with the Helsinki Declaration or with the Ethical Guidelines for Clinical Trials. Consequently, this Committee comprises not only medical science experts from JGOG members but also authorities of ethics or laws as non-JGOG members and citizen members that are assumed to widely reflect the general opinion of human specimen providers on human rights. This Committee should be independent from any site-specific committees to adhere to neutrality. Most importantly, this Committee exercises surveillance over a clinical trial so that human subjects should not suffer disadvantages from participation in the trial and their trial participation should not be tacitly forced by medical care providers.

I introduce next the Facility Certification Committee, which is obliged to guarantee the quality of facilities that wish to join JGOG studies. Facilities that intend to join a multi-facility joint clinical trial performed under the auspices of JGOG have to meet requirements of the Helsinki Declaration or the Ethical Guidelines for Clinical Trials. Those facilities need, first of all, to be so organized as to be capable of defending human rights. Therefore, all people engaged in JGOG clinical studies are obligated to report Roster Forms, COI status, and to be educated about ethics.

It is one of JGOG's missions to perform clinical studies at the international level, which is supported by both the Ethics Committee and the Facility Certification Committee that are the heart and soul of JGOG. It is not guaranteed that human subjects can participate in a study of concern without anxiety unless the quality of the study is guaranteed by securement of the quality of participating facilities and human rights are safeguarded.

## About JGOG's activities



# Facility Certification Committee: Greeting and Report of recent events

Kaneyuki Kubushiro, M.D., Ph.D. Chairperson, Facility Certification Committee

I consider it a great honor to have been appointed as Chairperson of the 2011 Facility Certification Committee of JGOG and look forward to JGOG members' continued cooperation.

JGOG is obliged to put multi-facility joint clinical trial projects into operation for the purpose to establish and spread the most appropriate chemotherapeutic approach to the treatment of gynecologic malignant tumors. Such projects should be conducted by reliable facilities where an institutional review board (IRB) and an ethics committee have been set up and quality control of trials is secured. The Facility Certification Committee is obligated to screen facilities that wish to participate in a project through requisite inspections so that only trustworthy facilities as above are certified for participation in a multi-facility joint clinical trial project.

In the last fiscal year, this Committee, under the leadership of the former chairperson, Prof Aoki, revised or arranged systems of facility certification, including revision of the facility certification criteria, application of the new JGOG point system, arrangement of rosters, application forms from a facility, and consent forms. These reorganizations are very important for quality control to be exerted in individual facilities. Accordingly, application

forms as well as consent forms for facility certification have been revised. Major revisions are declaration of IRB set up and necessitating an exchange of agreement forms as to implementation of a trial project between JGOG and each participating facility in addition to contents of the conventional registration application form to be filled out by an applicant.

Furthermore, for JGOG to participate in international joint clinical trials, JGOG rosters have to be arranged according to demands of GOG and GCIG or they have to be in agreement with "the Ethical Guideline for Clinical Trials (the Ministry of Health, Labour and Welfare)." This process is important for securing trust in a JGOG clinical trial.

Revised application forms for new facility participation have been in effect since January 2011, but renewal application forms for current participating facilities since May 2011.

This Committee is active in trying to adapt clinical trials to the Ethical Guideline for Clinical Trials and to secure international trust in JGOG clinical trials. I would appreciate JGOG members' support.

About JGOG's activities



## Ethics Committee

Toshiko Jobo, M.D., Ph.D. Chairperson, Ethics Committee

It was in April 2004 that the JGOG Ethics Committee was inaugurated. Its aims are assumed to examine ethical appropriateness of medical researches and medical practices based on the following guiding principles: "Helsinki Declaration," "The Appropriate State of Research/ Development Using Human Tissues Removed during Operation," "Ethical Guidelines for Researches on Human Genomic and Genetic Analyses," and "Ethical Guidelines for Clinical Trials." There is a rule that the Committee comprise seven or more members, including one or more female members as well as members outside JGOG. A researcher in charge of a JGOG's clinical trial is required to submit an implementation program (a proposal), a document of informed consent (a proposal), and a survey sheet (a proposal) which must undergo examination by the Ethic Committee.

Apart from ethical examination of clinical trials, seminars on ethics have been given to JGOG members at annual general assemblies since 2006. A lot of the members attended at lectures, including "Psycho-oncology useful for clinical trials" given in 2010 by Dr. Akira Ohshima of the Kyushu Cancer Center and "Guidelines for management of a conflict of interests (COI) in Health and Labour Sciences Researches" in 2009 by Dr. Jun Sakamoto, Minister's Secretariat of the Ministry of Health, Labour and Welfare.

The Ethics Committee will maintain collaboration with the Clinical Trial Review Committee and will continue ethics education for the members so that future clinical trials can be implemented smoothly.

Strategy against gynecologic cancer: past, present, and future.  
-Cervical Cancer (Vulva Cancer) Committee-



## On the past clinical trials of the JGOG Cervical Cancer (Vulva Cancer) Committee, especially JGOG1066

Takafumi Toita, M.D., Ph.D. Provisional member of the Cervical Cancer (Vulva Cancer) Committee

The JGOG Cervical Cancer (Vulva Cancer) Committee has conducted several clinical trials that have contributed to our understanding of treatment of cervical cancer. This article presents a preliminary summary of a recently completed trial, "Phase II study on concurrent chemoradiotherapy (CCRT) using high-dose-rate intracavitary brachytherapy (HDR-ICBT) in locally advanced uterine cervical cancer : JGOG1066."

Concurrent chemoradiotherapy (CCRT) was investigated in randomized clinical trials conducted in the United States, and is now globally regarded as a standard therapy for patients with advanced localized cervical cancer. However, the Japanese

guideline for cervical cancer published in 2007 gave CCRT a grade B recommendation. Two critical clinical questions need to be answered for CCRT to be applied as standard therapy (ie, grade A recommendation) in Japan.

First, some Japanese physicians have been concerned about the feasibility of the standard chemotherapeutic regimen when used in Japanese women. GOG120 set the global standard chemotherapy regimen of weekly administration of cisplatin at a dose of 40 mg/m<sup>2</sup>. In Japanese clinical practice, the cisplatin dosage is often

appropriately reduced for fear of its potential toxicity. However, this type of modification might compromise the therapeutic efficacy. Therefore, we considered that the feasibility and toxi-

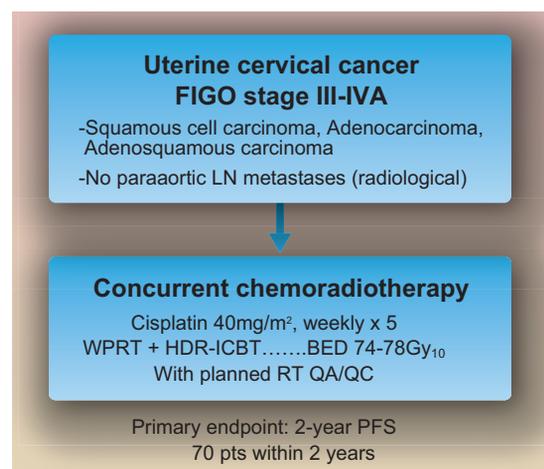


Figure 1

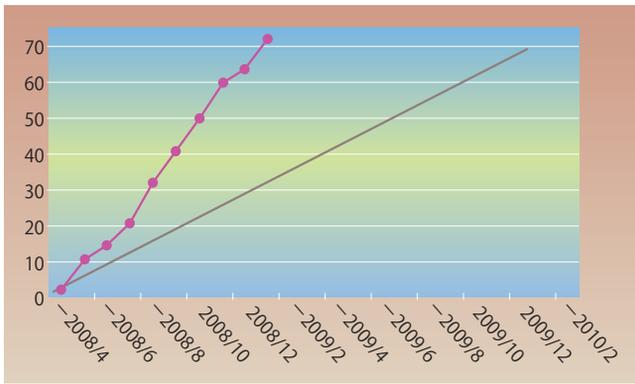


Figure 2

city profile of the standard regimen should be prospectively investigated in Japanese women.

Second, both safety and efficacy of high-dose-rate intracavitary brachytherapy (HDR-ICBT) need to be evaluated in the setting of CCRT. The earlier GOG and RTOG trials adopted only low-dose-rate intracavitary brachytherapy (LDR-ICBT). However, almost all Japanese healthcare institutions utilize HDR-ICBT in the treatment of uterine cervical cancer. Clinical application of HDR-ICBT has been recently increasing globally, including in the US. Several pilot studies suggested acceptable safety as well as efficacy with the use of HDR-ICBT in CCRT. Although recent GOG and RTOG clinical trials also permitted HDR-ICBT application, only limited clinical data are currently available from them. Based on this background, we considered prospective investigation of the efficacy as well as the toxicity of HDR-ICBT in the CCRT to be warranted. To address these two clinical questions, the phase II multi-institutional clinical trial, JGOG1066, was conducted.

EORTC, etc) have already established appropriate radiotherapy QA/QC systems. In JGOG1066, radiation oncologists were involved not only in developing the protocol but also in the radiotherapy QA/QC process. This is the first JGOG study in which radiation oncologists were extensively involved, and they made substantial contributions. Using the methods of GOG as reference, the JGOG Radiotherapy Committee played a pivotal role in the radiotherapy QA/QC process, including credentialing and individual case review. Future JGOG CCRT trials should follow the above process to help guarantee the quality of trial results.

Patient accrual started in March 2008 and the planned number of cases completed registration within 10 months. This accrual period was considerably shorter compared with the 2 years that as planned (Figure 2). The preliminary analyses showed that toxicity was almost within tolerable limits and the therapy completion rate was excellent. These results suggest that CCRT using the global

standard cisplatin regimen may also be feasible for use in Japan.

Collection of final follow-up information has been completed and all data are currently being analyzed. The primary endpoint, 2-year progression-free survival rates, is to be reported along with secondary endpoints such as late adverse events in a few days.

Although the radiation therapy protocol adopted in this trial was almost the same as the Japanese standard, it differed from the US and European standard in two aspects: this study used central shielding for external pelvic irradiation and lower total doses (external beam plus ICBT) to the central tumor. If data analysis shows that locoregional control demonstrated in this study is comparable to that of the global standard radiation dose, this radiotherapy regimen is expected to be regarded as one of the standards in CCRT.

Some important international joint trials using CCRT are now underway in the Gynecologic Cancer Intergroup (GCIG). JGOG strongly wishes to join these trials, but it is hard to do so because the radiation doses used are too high for small Japanese women to receive safely. If data from JGOG1066 show that a lower radiation dose is equally efficacious as that being used in the international joint trials, it is expected that a reduction of the per-protocol radiation dose will be allowed so that JGOG can participate in international trials.

Whole pelvis irradiation has been given to high-risk patients who have undergone radical surgery for cervical cancer in the West as well as our

Strategy against gynecologic cancer: past, present, and future.  
-Cervical Cancer (Vulva Cancer) Committee-



## The Cervical Cancer Committee is Grappling with Gynecologic Cancer: Present, Past, and Future With Respect to the Ongoing Clinical Trial, JGOG1067

Ken Takizawa, M.D., Ph.D. Ex-Chairperson, the Cervical Cancer (Vulva Cancer) Committee

The Cervical Cancer Committee of JGOG is now performing a phase II clinical trial entitled as “Usefulness of Postoperative Chemotherapy for

Cases That Underwent Radical Surgery for Cervical Cancer and Are Positive for Lymph Node Metastasis” (referred to as JGOG1067).

Whole pelvis irradiation has been given to high-risk patients who have undergone radical surgery for cervical cancer in the West as well as our

country as if it were common sense. It can, however, trace its roots back to the 1930's and starting from a clearly insufficient dose as reviewed now (30-40 grays) of roentgen radiation. No prospective study has ever been done thereafter in our country to compare surgery alone with surgery plus postoperative irradiation in high-risk patients. A majority of Japanese leaders of gynecologic oncology have stuck to such radiotherapy in the belief that postoperative irradiation must be useful as long as irradiation regimens are improved or radiotherapy is limited to intermediate or high-risk patients.

It really makes me feel sorry that postoperative irradiation has been prescribed even after perfect radical total hysterectomy only to reduplicate loads on patients based on belief or reconsideration: "Postoperative irradiation is a matter of course if there is a risk of imperfect hysterectomy since perfect surgery inclusive of pelvic lymphadenectomy shouldn't have been done" and "Sorry and ashamed that a recurrence might occur from a surgical field (the pelvis) which was operated on for a radical cure."

Even such high-risk patients as had lymph node metastasis were unlikely to undergo postoperative radiation after Meigs' radical total hysterectomy in fear of post-irradiation adverse events such as frozen pelvis, intestinal obstruction etc. before the earlier 1970's when Dr. Meigs, who was

father of cervical cancer surgery in the US, and surgeons who learned directly from Dr. Meigs were active. In the latter half of the 1970's when Meigs' surgery came to be downscaled, it seems that not only high-risk but also intermediate-risk patients were treated with postoperative radiotherapy.

Western surgeons may now take it for granted that postoperative patients with cervical or uterine body cancer, if assessed at intermediate or high-risk, should undergo postoperative radiotherapy, since their radical surgery for these cancers, except in Italy and a part of the US, is obviously less extensive than ours.

In our country, prospective comparative studies of postoperative irradiation and postoperative chemotherapy (CAP therapy) for the treatment of uterine body cancer patients at intermediate- to high-risk were initiated in the latter half of the 1990's. As soon as no difference in efficacy between the two treatment groups was confirmed midway through the studies, there occurred a shift like an avalanche from postoperative irradiation toward postoperative chemotherapy in 2000 and later. Now, as the adjuvant therapy for uterine body cancer, postoperative chemotherapy is performed in a majority of institutions for the probable reason that surgical methods of our country are clearly extended compared to those of the West, giving a feeling that post-irradiation sequelae like

intestinal obstruction and lymphedema are worse.

I am quite puzzled why such a shift toward postoperative chemotherapy as has occurred in the treatment of uterine body cancer does not take place in cervical cancer. Postoperative CCRT was supported only by Peters' paper, nevertheless Japanese gynecologists share the way of thinking that patients with pelvic lymph node metastasis should be managed with postoperative CCRT. I am therefore compelled to wonder whether they are confident in their technique of radical total hysterectomy.

Now, JGOG1067 explores values (in terms of 2-year aggravation-free survival rates, adverse events, so on) of two brands of anticancer agents (CPT-11 and Nedaplatin), both of which have been developed in our country, for postoperative chemotherapy in uterine cervical cancer patients who have received radical surgery and yet have pelvic lymph node metastasis. This trial started one and a half years ago, having registered at last 43 of the registration goal of 63 cases. I hope that the registration goal shall be achieved as soon as possible and the agents' usefulness shall be demonstrated as expected. Then, a phase-III trial to compare postoperative irradiation (probably CCRT) and postoperative chemotherapy will be planned. Such a shift like an avalanche as was experienced in uterine body cancer is expected to happen.

Strategy against gynecologic cancer: past, present, and future.  
-Cervical Cancer (Vulva Cancer) Committee-



Future Directions

Mikio Mikami M.D., Ph.D. Chairperson, Cervical Cancer Committee

The Cervical Cancer Committee of JGOG surveyed the therapeutic practice for treating uterine cervical cancer among hospitals participating in JGOG at the end of 2010. This survey clarified the treatment plans of each

JGOG hospital, and identified those for which there are no clear recommendations in the JSOG treatment guideline. The survey was aimed at identifying potential new topics for clinical trials in cervical cancer in Japan. We dis-

patched questionnaires to 199 hospitals participating in JGOG and got answers from 166 of them, for an overall response rate of 83.4%. When we analyzed the answers in the questionnaires, some large differ-

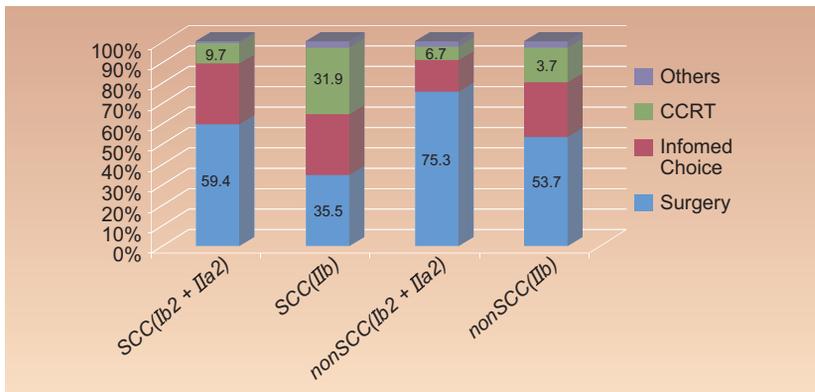


Figure1 Treatment Plan for patients with Cervical Cancer Staged Ib2, IIa2 and IIb

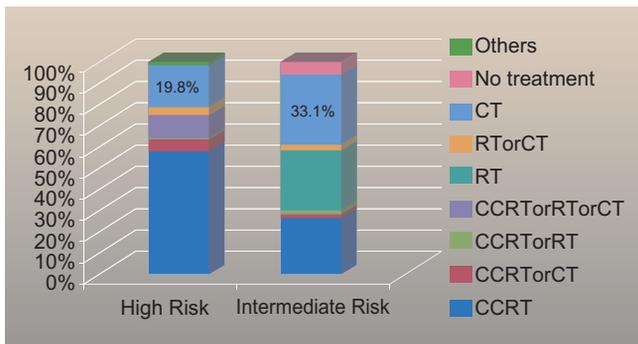


Figure2 Postoperative adjuvant therapy

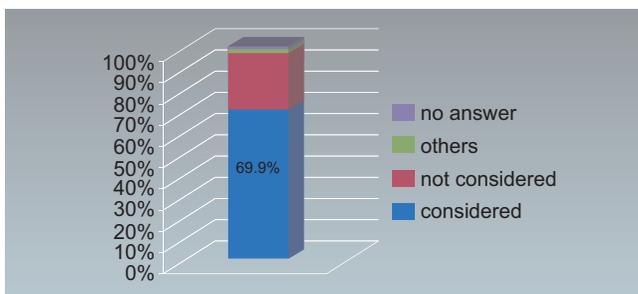


Figure3 Histological type should be considered differently

ences between treatment of uterine cervical cancer in Japan and several overseas treatment guidelines became clear. We will report some of them. There is only a mention of CCRT as a treatment option for patients staged IIb in guidelines of NCI, NCCN and ESMO. However, only surgery is

mentioned in a guideline of AGO. Both surgery and CCRT are mentioned in the Japanese guideline. In the questionnaire, replies were largely divided into surgery and CCRT (Figure 1). In Japan, the standard procedure for radical hysterectomy was first established by Professor Okabayashi (Kyoto University). As a result of improvement of instrumentation and new ideas of many older gynecological oncologists, radical hysterectomy is now established as a highly sophisticated technological operation. Thus, the concept and practice of the advanced radical hysterectomy are based on the past efforts of numerous traditional gynecological oncologists.

After surgery, patients are classified into groups of low, intermediate or high recurrence risk based on postoperative pathological examination, and a post-surgery treatment plan is selected. Generally, radiotherapy or CCRT is recommended for patients with high or intermediate recurrence risk. However, many JGOG participating hospitals performed only post-operative chemotherapy (Figure 2). The reason for this is probably that it is very likely that delayed side effects, such as aggravation of lymphedema and ileus, can occur after postoperative radiotherapy.

Squamous and adenocarcinoma are treated identically in Europe and USA. Therefore, there is no clinical study available that considers pathological types. In contrast, it was recognized that about 70% of JGOG participating hospitals thought that adenocarcinoma belonged in a particular group (Figure 3). There are only a few clinical studies published on adenocarcinoma, and there is no definite evidence showing what kind of therapy is most effective for patients with adenocarcinoma. A nationwide clinical study should be started, and it is to be hoped that more factual information about cervical adenocarcinoma would be developed in Japan in the future.

The Japanese original way of thinking about cervical cancer treatment became clear as a result of these questionnaires. Based on such results, we would like to plan prospective and retrospective studies together with JGOG members.

## Editorial postscript



The Nebuta Festival in Aomori

The predecessor of the Japanese Gynecologic Oncology Group (JGOG) was established in 1981 as a study group for cervical cancer, and it changed the name to JGOG in 2002. JGOG was certified as a specified non-profit organization, and the group expanded nationwide and undertook studies to establish the optimal chemotherapy for patients with gynecologic cancer besides cervical cancer. Furthermore, the study fields were expanded into surgery, radiotherapy, and examination for detection of gynecologic cancers. JGOG has organized several committees and is now the largest study group for gynecologic cancer in Japan. In this issue, we look back on the progress of JGOG studies regarding cervical cancer.

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Chairperson, Public Relation Committee



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