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Newsletter of the Japanese Gynecologic Oncology Group (JGOG)

## Table of Contents

The JGOG Action Plan for the Year 2011 – 2012 ----------Kazunori Ochiai 1

***Supporting committees***

Data Management Committee ----------Noriyuki Katsumata 2

Radiotherapy Committee ----------Takafumi Toita 3

Pathology Review Committee ----Teiichi Motoyama 3

Clinical Trial Audit Committee ----------Hidetaka Katabuchi 4

***Introduction to JGOG Clinical Research***

JGOG1067----------Nobuhiro Takeshima 4

JGOG3018----------Tsutomu Tabata 5

***About JGOG's activities***

Report of the 9th Annual Meeting of JGOG ----------Masayuki Hatae 6

# The JGOG Action Plan for the Year 2011 – 2012

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

After new members of the board of directors were elected at the general assembly last year, the new Board Meeting, which was held on January 22, 2011, re-elected me as Chairperson of the Board. It is my great honor to assume the weighty responsibility again. I take this opportunity to show the 2011 – 2012 Action Plan of JGOG not only to JGOG members but also to our friends of foreign related organizations.

Nothing is more important for JGOG than execution of high-quality clinical studies. We will set up the following action goals to produce internationally-accepted level of fruits.

1) Creation of appealing protocols

An appealing protocol is just the first step toward an excellent clinical study. Conducting a review of gynecologic oncology trends of the world, we will build protocols that are internationally attractive. We will also hold open discussions for protocol planning so that JGOG members can be directly involved in the process.

2) Raising members' awareness

JGOG consists of members, who should be proud of being a member of this study group. Therefore, individual members are required to have self-awareness, responsibility, and global qualifications for clinical studies. JGOG will help them try to meet these requirements.

3) Improvement of the quality of participating institutions

System maintenance and improvement of individual participating institutions are essential for execution of high-quality clinical studies. Audits are properly performed to educate them through and through.

4) Collaboration with international clinical trials

International collaboration will be more and more important. JGOG3017 is an international collaborative clinical trial in cooperation with GICG and it has already finished a predetermined number of case registrations. We will do our best to promote future international clinical trials in conjunction with foreign researchers so that our study group, JGOG, can fulfill the expectations of the international community.

5) Promotion of younger gynecologic oncologists' education

Younger gynecologic oncologists are indispensable for the maintenance of JGOG as an organization with persistent vitality. It is one of our important projects to educate the next generation of research leaders who deeply understand what clinical studies are. For this purpose, educational seminars as well as opportunities to study overseas are provided.

6) Support of backup divisions required to execute clinical studies

Backup divisions comprise the data center, the data manager, clinical statisticians, pathologists, radiologists, the Secretariat of JGOG, and others. We try to improve the organization so that a lot of supporters of organization businesses as well as of clinical studies can efficiently work as a specialist.

7) Promotion of publicity activities

We will conduct a public relations campaign by means of content-rich open lectures for citizens and enriched quality of the website, and through the Chemotherapy Newsletter.

8) Promotion of exchanges with patients

Clinical studies would not be successfully feasible without patients participating in them as a subject. We will exchange views with patients who decide by themselves to participate in researches to listen to them. Their opinions, thus, will be incorporated in JGOG projects.

9) We aim at ensuring open JGOG

JGOG will disclose its projects so that contents of its activities can be fairly evaluated. We will improve the conference system to make conferences public as much as possible and to make conference minutes available for public inspection.

10) We will organize JGOG projects to look for more efficiency in the JGOG operation.

We will always reconsider a large variety of projects to try to streamline our enlarging organization so that expenses for proper projects can be increased.

Above mentioned goals may rarely be achieved in a short period of time but we have to make steady progress one step at a time as before. We ask for tremendous support to JGOG.

Supporting committees

# Data Management Committee

Noriyuki Katsumata, M.D., Ph.D. Chairperson, Data Management Committee

The Data Management Committee was organized to operate for the data management of JGOG clinical trials. Clinical trials should be designed and conducted properly based on ethics and science, and quality assurance and control for data management is important for the results which may contribute to the treatment for cancer patients.

We collaborate the Data Center of JGOG with Department of Clinical Study Coordination, Research Center for Clinical Pharmacology, the Kitasato Institute. The Data Center is engaged in registration, assignment, data monitoring, data management, auditing, and statistical analyses. The Data Management Committee is engaged in the development of rules for data management.

The Data Management Committee has so far evaluated rules as well as procedures for safety information management of JGOG clinical trials and monitoring reports. It also developed procedures of report conveyance. In order to promote registration, e-mails to report progress of clinical trials are now accepted at all times. The Committee issues periodically the Data Center Newsletter. Institutes that wish to join JGOG tend to increase every year. Hopefully, a problem for future solution is to have JGOG members submit CRF (Case Report Form) timely and to improve its quality.

We will continue to confer actively to improve the quality of JGOG clinical trials.

Supporting committees

# Radiotherapy Committee

Takafumi Toita, M.D., Ph.D. Chairperson, Radiotherapy Committee

Radiotherapy plays an important role in multidisciplinary treatments of gynecological cancers. To obtain scientifically valid results from clinical trials, it is essential to develop appropriate radiotherapy protocols and a quality assurance (QA) system. The JGOG Radiotherapy Committee was organized in 2007 to accomplish this goal. The committee consists of nine radiation oncologists with expertise in the gynecological oncology field. We have already accomplished important first steps with JGOG1066 in locoregionally advanced cervical cancer patients. JGOG1066 was a phase II study to test the feasibility and efficacy of concurrent chemoradiotherapy (CCRT), using a standard worldwide chemotherapy regimen (weekly cisplatin 40mg/m2), and standard Japanese radiotherapy schedules with high-dose-rate intracavitary brachytherapy (HDR-ICBT). For this study, the committee developed radiotherapy protocols based on current Japanese standard clinical practice and performed credentialing of participating institutions. To assess compliance with radiotherapy protocols, the committee also performed an individual case review for each of the study patients.

Recently, there has been rapid progress in radiotherapy techniques, which include intensity-modulated radiation therapy (IMRT), image-guided radiotherapy (IGRT), and image-guided brachytherapy (IGBT). These novel treatments cannot be safely applied to gynecological cancer patients without appropriate radiotherapy QA. We plan to develop radiotherapy protocol templates which will include both QA and quality control (QC) programs for application in future JGOG trials.

For participation in global studies that include radiotherapy, the committee also has another important mission, which is to develop actually standard radiotherapy methods to be accepted in world wide, in collaboration with international study groups.

Supporting committees

# Pathology Review Committee

Teiichi Motoyama, M.D., Ph.D. Chairperson, Pathology Review Committee

The Pathology Review Committee is supporting the JGOG3017 study, which is a randomized Phase III trial to compare the survival impacts of paclitaxel plus carboplatin (TC) therapy and irinotecan plus cisplatin (CPT-P) therapy as first line chemotherapies for clear cell adenocarcinoma of the ovary. The membership of our committee consists of 15 Japanese pathologists. In addition, Dr. Silverberg, USA, Dr. Kim, Korea, Dr. Lostio, Italy and Dr. Millan, UK join us at the review of central pathology. Pathologic diagnoses are finally decided through prior reviews using virtual slides on a Web system and via Web system conferences. Central pathology reviews have been carried out in 343 registered cases. Approximately 94% of them were considered to be qualified.

# Clinical Trial Audit Committee

Hidetaka Katabuchi, M.D., Ph.D. Chairperson, Clinical Trial Audit Committee

The Clinical Trial Audit Committee was established in 2006 and finished 44 door-to-door inspections at 39 institutions as of December 2010.

Around the beginning of inspection system, number of registered cases in the JGOG clinical trial was highly interested. In contrast, less attention was paid to the implementation procedure or the improvement of the quality; consequently, the majority of inspected institutions were judged to have "important problems" because of inappropriate custody of consent forms, or insufficient records of treatment evaluation including eligibility and adverse events. Recently, institutions that were first judged to have "important problems" were surely reduced in number along with their enhanced understanding of the improvement of the quality. Additionally, their appreciation of the quality was deepened through the Committee's repeating inspections and also through their sharing of these problems. However, there still remain to be several institutions to need to improve in their clinical trials although not given a decision of "important problems".

At the present time, a hundred or more institutions are participating in JGOG clinical trials, but inspection was not accomplished in less than a half of them. As an important role to play for "quality control" of the whole clinical trials, the Committee needs to start newly an annual inspection of an increasing number of institutions and to come up with a good way to continuously inspect after their first inspection was accomplished.

Moreover, regarding clinical trials that were initiated after the Ethics Guidelines for Clinical Trials took effect in April 2009, the Committee is planning to add the following items to surveilance of participating institutions: IRB system, circumstances of reporting progress situations or severe adverse events to presidents of institutions, and situations of educating investigators about clinical trials as well as ethics.

Introduction to JGOG Clinical Research

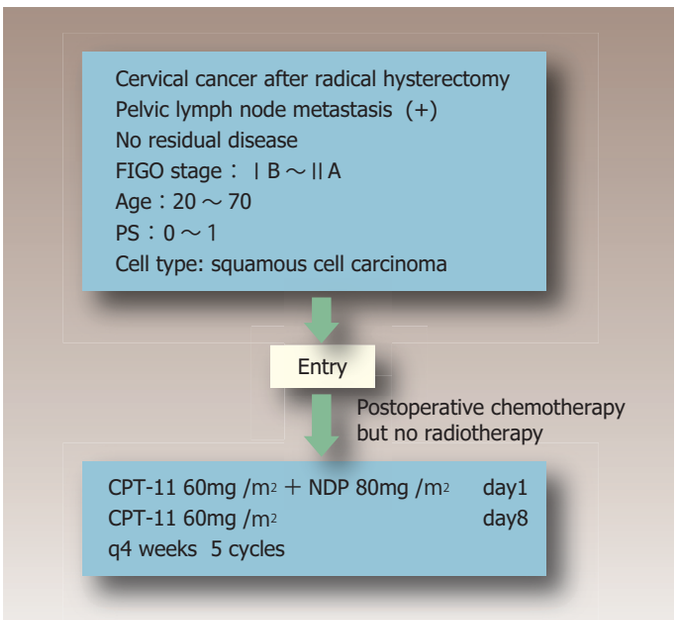
# A phase II study of adjuvant chemotherapy with Irinotecan (CPT-11) plus Nedaplatin (NDP) for stage Ib2 or IIa node-positive cervical cancer; JGOG1067

Nobuhiro Takeshima, M.D., Ph.D.
*Cancer Institute Hospital*

Although radiotherapy (RT) or concurrent chemoradiotherapy (CCRT) is generally accepted as postoperative therapy for intermediate- or high-risk cervical cancer, several studies have suggested the utility of chemotherapy (CT) alone. Postoperative CT for cervical cancer confers the following benefits: 1) it is considered to be the most powerful way to eradicate subclinical distant metastases; 2) it provides a better postoperative quality of life by precluding radiation-related morbidity such as small bowel obstruction or leg edema; and 3) local recurrence can be salvaged with RT or CCRT.
For intermediate-risk cervical cancer, several studies have reported excellent survival rates by the use of CT alone, suggesting that postoperative CT could be used as the first choice for patients with intermediate-risk disease. For high-risk cervical cancer, however, the use of postoperative CT may be more challenging. Previous studies together with our data suggested that the 5-year survival rate could be more than 80% even in high-risk patients. More recently, we reported on 46 patients with stage IB2～IIB cervical cancer who were treated by neoadjuvant chemotherapy (NAC) followed by radical hysterectomy plus postoperative CT but without receiving RT. The reported 3-year progression-free survival was 86%. The combination of NAC and postoperative CT can totally exclude RT-related morbidity. Clinicians can also deduce the chemosensitivity of each tumor by evaluating the NAC response, and we believe that this might help

in choosing the postoperative therapy. Conversely, the biggest concern with such non-RT postoperative therapies is that local recurrence may increase in the absence of RT. Previous studies, in which CT alone was used postoperatively, reported that the rate of pelvic recurrence was acceptable and that 45～50% of the pelvic recurrence was salvaged by RT. However, all of these reports were based on retrospective studies, so a new prospective study on this aspect of the therapy has been requested.

Based on these observations, we have started a new JGOG trial regarding postoperative CT for cervical cancer. In this study, both the beneficial effects and the adverse toxic effects of adjuvant CT with Irinotecan (CPT-11) plus Nedaplatin (NDP) for node-positive cervical cancer are studied in a phase II setting. The primary endpoint is relapse-free survival in 2 years. Secondary endpoints include incidence of morbidity, completeness of chemotherapy, overall survival in 5 years, relapse-free survival in 5 years, and incidence of leg lymphedema. The target sample size is estimated to be 63 cases.




Introduction to JGOG Clinical Research

# Randomized phase III trial comparing pegylated liposomal doxorubicin (PLD) at 50mg/m² versus 40 mg/m² in patients with platinum-refractory and -resistant Mullerian carcinoma (epithelial ovarian, fallopian tube, or primary peritoneal carcinoma ); JGOG3018

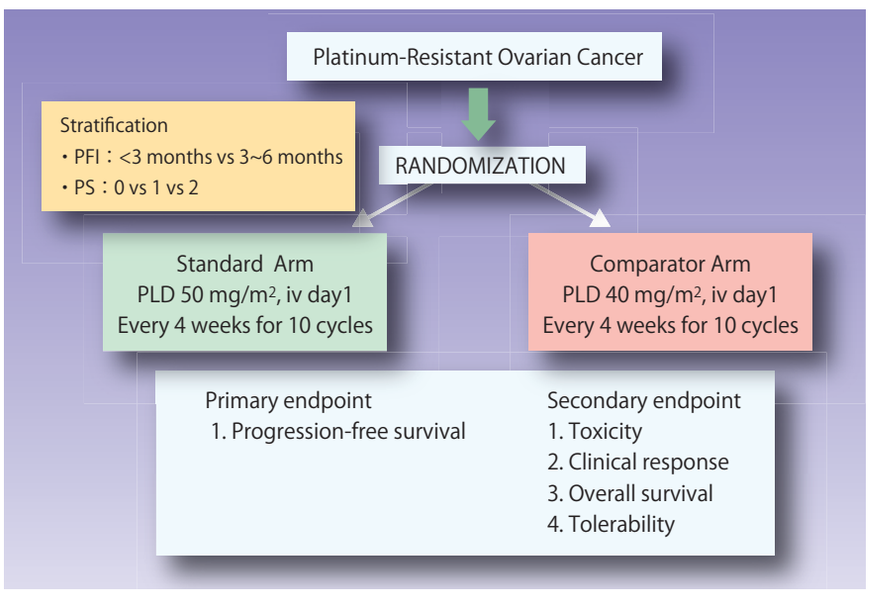
Tsutomu Tabata, M.D., Ph.D.
*Mie University Hospital*

Safety and tolerability are main objectives in the treatment of patients with recurrent ovarian cancer. Single-agent pegylated liposomal doxorubicin (PLD) has been used as one of the standard chemotherapy regimens for platinum-resistant ovarian cancer. The US Food and Drug Administration and the Japanese Ministry of Health, Labour and Welfare approved a PLD dosing schedule of 50 mg/m² every 4 weeks, and this scheduling has now achieved worldwide approval. Based on some retrospective studies, it has been suggested that the incidence of palmar-plantar erythrodysesthesia (PPE) would be higher in patients receiving PLD at 50 mg/m² rather than 40 mg/m², and that specific side effects, such as PPE, of PLD at standard doses may severely alter the quality of life in patients with recurrent ovarian cancer. However, it is unclear whether progression-free survival is equivalent for the two PLD regimens (40mg/m² and 50mg/m²). Therefore, we are now conducting a Phase III randomized, multicenter, non-inferiority study comparing progression-free survival of patients with platinum-refractory and -resistant Mullerian carcinoma (epithelial ovarian, fallopian tube, or primary peritoneal carcinoma) treated with 50 mg/m² versus 40 mg/m² PLD ( JGOG3018).

The patients with platinum-refractory and -resistant Mullerian carcinoma are enrolled in two subsequent multi-

center phase III studies with identical study design. Patients are treated with PLD 50 mg/m$^2$ monthly or PLD 40 mg/m$^2$ monthly and are evaluated monthly for toxicity and tumor response. Treatment is continued unless progression of disease or unacceptable toxicity is observed. Main selection criteria are: Platinum-refractory and -resistant Mullerian carcinoma (epithelial ovarian, fallopian tube, or primary peritoneal carcinoma); measurable disease; at least 1, maximum 2 pretreatments; age 20-79 years; PS 0-2; sufficient hematological and organ function. A primary endpoint is progression-free survival and secondary endpoints are overall survival, toxicity profile, clinical response and tolerability. The target total number of patients in this trial is 412.

The PLD dose of 50 mg/m$^2$ has received worldwide approval; this is the standard dose. For a PLD dose of 40 mg/m$^2$ to become the standard dose, we believe a non-inferiority study comparing 40 mg/m$^2$ to 50 mg/m$^2$ in patients with recurrent ovarian cancer is needed. Of course, we expect to see advancements in anti-neoplastic strategies that are effective and relatively safe and that will improve survival and quality of life of all patients with cancer. However, evidence-based medicine aims to apply the best available substantiation gained from scientific studies to clinical decision making. We should seek to assess the strength of evidence regarding the risks and benefits of various treatment options (including decisions not to treat). Therefore, we believe that the GOG 209 trial provides an ideal opportunity to clarify whether a reduced dose of PLD does not compromise the survival benefit to patients. The GOG 209 trial compares the GOG standard chemotherapy arm for advanced endometrial cancer, which is a combination of paclitaxel, doxorubicin, and cisplatin, with a community standard regimen of paclitaxel plus carboplatin. In Japan, PLD was approved for recurrent ovarian cancer in 2009. Therefore, it is acceptable to conduct such a comparative trial, since PLD constitutes a relatively new approach for both gynecologic oncologists and patients. Based on this background, the Japanese Gynecologic Oncology Group has now opened this trial (JGOG3018). Until the result of this trial becomes available, the standard dose of PLD should not be changed.




About JGOG's activities

# Report of the 9th Annual Meeting of Japanese Gynecologic Oncology Group

Masayuki Hatae, M.D., Ph.D. Vice President, JGOG

The acronym "JGOG (Japanese Gynecologic Oncology Group)" used to include 'chemotherapy' as written in kanji before the 9th meeting, but at that meeting 'chemotherapy' was no longer included in kanji. This change was done because trial targets would be extended not only to chemotherapy-based clinical trials but also to diagnostic studies, radiation therapy, and pathologic diagnosis in order to elucidate clinical questions as well as therapeutic fundamentals. Moreover, JGOG accomplished steadily the following duties during the past year: Introduction of COI, preparation of a Roster, and activitiy of the Clinical Audit Committee.

Undoubtedly, cooperation with GOG played a leading role in JGOG's 10-year uninterrupted participation in international joint trials in addition to its routine national trials. Through our international participation, we have built an essential system for trial performance which has greatly influenced the present status of JGOG. During the period when the system was developed, drug development trials were enormously transformed, especially those for molecular targeting drugs. Strategies for international joint drug development trials are being established in order to rapidly and efficiently achieve valuable results in the midst of a large number of new drugs under development.

Among a variety of cancers targeted for clinical trials, gynecologic tumors, especially ovarian cancers, are most likely to be targeted, although the total number of these tumors is smaller than that of any other tumor. Therefore, these tumors have a tendency to escape from being subject in clinical trials of a molecular targeting drug, so that we have to manage to remove this bottleneck in the introduction of this type of new drugs to the clinical setting.

Regarding clinical trials, on the other hand, JGOG 1065 and 1066 were completed under the Cervical Cancer (Vulva Cancer) Committee, and 1067 is steadily collecting cases. JGOG1068 to evaluate NAC is being arranged. The Uterine Corpus Cancer Committee had results of JGOG2041, 3 arm phase II study, published in Annals of Oncology and will finish data collection for JGOG2043 before long. NAC therapy for advanced endometrial cancer and a new trial for the treatment of uterine carcinosarcoma are now under consideration. The Ovarian Cancer Committee is engaged in GCIG/JGOG3017 to treat ovarian clear-cell carcinoma, which is close to the end of data collection. It is hoped that this trial will provide important results as an international study in which Japan took the initiative.

Furthermore, we started a comparative study with intraperitoneal (IP) vs. intravenous (IV) chemotherapy, taking into account dose-dense TC based on JGOG 3016 results. We believe that this study will be important by stating a clear clinical position in IP chemotherapy that is different from complicated trials performed in Europe and the US. This phase III study is being carried out to determine the validity of IP chemotherapy for ovarian cancer. In addition, a phase III trial with Pegylated Liposomal Doxorubicin 40 mg/m$^2$ vs 50 mg/m$^2$ is in progress. A study to validate adjuvant chemotherapy for early ovarian cancer after systematic debulking surgery is also under consideration.

The Clinical Trial Audit Committee, GOG Japan Committee, GCIG Committee, Education Committee and other committees will be trying hard to improve the quality as well as provide information of clinical trials in cooperation with these committees.


**We here would like to introduce that the 9th Japanese Gynecologic Oncology Group Annual Meeting (General Assembly) was held according to the following program.**

## The 9th Japanese Gynecologic Oncology Group Annual Meeting (General Assembly)

**Time: Nov 26, 2010 (Fri). 9:00 – 17:50**
**Place: Diamond Room, 2nd floor, Hotel Grand Palace**

**Opening Remarks** (9:00 - 9:10) — President Kazunori Ochiai

**I. Business Report**

1. Committee Report (9:10 - 9:20) — MC & Vice President Yasuhiro Udagawa
   (Questions to the Annual Report distributed in advance)
2. Education Committee (9:20 - 10:00) — MC & Chairperson Noriaki Sakuragi
   1) Overseas Assignment Report
   2) Education Seminar Report

3. Quality Control of Registered Institutions (10:00 - 11:00)

| | | |
|---|---|---|
| | MC & Vice President | Masayuki Hatae |
| 1) Clinical Trial Audit Committee | Chairperson | Hidetaka Katabuchi |
| 2) Facility Certification Committee Report | Chairperson | Daisuke Aoki |
| 3) COI Committee Report | Chairperson | Toshiko Jobo |

-------*Coffee break* (11:00 – 11: 20)-------

**II. General Assembly**

| | | |
|---|---|---|
| 1. Opening remarks & Chairperson Selection | President | Kazunori Ochiai |
| 2. General Affairs Report | | JGOG Administration Office |
| 3. Amendment of the Articles of Incorporation | President | Kazunori Ochiai |
| 4. Fiscal 2009 Operation Report and Fiscal 2010 Operation Plan | President | Kazunori Ochiai |
| | Finance Officer | Makoto Yasuda |
| 5. Fiscal 2009 Statement of Revenues and Expenses (draft) and Fiscal 2010 Balance Plan (draft) | | |
| | President | Kazunori Ochiai |
| | Finance Officer | Makoto Yasuda |
| 6. Election of Members of the Board | President | Kazunori Ochiai |
| 7. Revision of the COI Guideline | Chairperson | Toshiko Jobo |

-------*Lunch break* (12:00 – 13:00)-------

**III. Disease Committee Open Discussion** (including Committee Reports) (13:00 – 16:30)

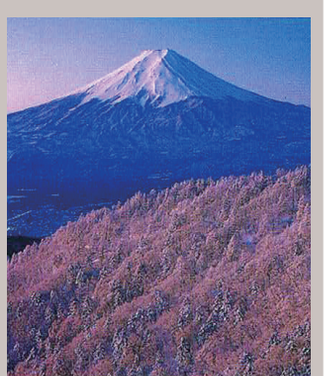
| | | |
|---|---|---|
| | MC & Vice President | Toru Sugiyama |
| 1. Uterine Cancer Committee Report (13: 00 – 14:00) | Chairperson | Ken Takizawa |
| 2. Cervical Cancer Committee Report (14:00 – 15:00) | Chairperson | Fumitaka Kikkawa |
| 3. Ovarian Cancer Committee Report (15:00 – 16:00) | Chairperson | Nobuo Yaegasi |

**IV. Domestic and Overseas Clinical Trials Executed or Supported by JGOG** (16:00 – 16:30)

| | | | |
|---|---|---|---|
| | | General MC & Vice President | Toru Sugiyama |
| 1. JGOG-Supported Clinical Trials to Develop Drugs | | Chairperson | Toru Sugiyama |
| 2. Collaboration with Foreign Organizations | GOG JAPAN | Chairperson | Junzo Kigawa |
| 3. Collaboration with Foreign Organizations | GCIG | Chairperson | Satoru Sagage |

**Closing Remarks** (17:45 - 17:50) Vice President Masayuki Hatae

## Editorial postscript



Mt.Fuji

JGOG was established with the aim of contributing to progress of cancer therapy through multi-institutional joint research projects to study optimum chemotherapy for cancer. Quality control of clinical trials holds a key to a guarantee for the quality of clinical trials designed to provide patients with the most appropriate chemotherapy.

The Data Management Committee, Radiotherapy Committee, Pathology Review Committee, and Clinical Trial Audit Committee are all the most essential committees to preserve the quality of clinical trials. Their functions were presented in JGOG International No. 4. Moreover, this Newsletter carries information on the JGOG1067 and the JGOG3018, one of ongoing Clinical Research projects.

We will continue making an effort to send the uninterruptedly high-level evidence to the world through the JGOG International. Please enjoy our JGOG International No.4.

**Kazushige Kiguchi** M.D., Ph.D.
Chairperson, Public Relation Committee

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