

Newsletter of the Japanese Gynecologic Oncology Group (JGOG)

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Function linkage

Toru Sugiyama, M.D., Ph.D. President, JGOG

The keyword of JGOG for the year 2017 is “function linkage”. It is “function linkage” among JGOG facilities and among researchers of KGOG and other Asian groups, and is also “function linkage” with data centers and bio banks.

We have created good academic partner relationships with data centers aiming at creating global standards of clinical research (investigator-initiated research and trials), with Translational Research Informatics Center (TRI, Director: Dr. Masanori Fukushima) being the core center and also with Kitasato University (Prof. Takaaki Takenaga) and Clinical Research Innovation and Education Center of Tohoku University Hospital (CRIETO, Director of Clinical Test Data Center: Prof. Takuhiro Yamaguchi). We will perform functional administration at the three institutes. In regard to JGOG organizational banks, we concluded a non-disclosure agreement with Tohoku Medical Megabank Organization of Tohoku University (ToMMo) on November 1, and are currently preparing a joint research agreement (JGOG/ToMMo Bio bank). At the same time, we will establish Translational Research Committee within Future Planning Committee under the council consisting of the president and vice-presidents. We plan to obtain approval for the Committee in the general meeting this year and officially start the Committee in the coming fiscal year. Accumulation of good-quality specimens as well as clinical data of gynecologic cancers will help JGOG members start translational research that will lead to future medicine.

JGOG registry contains 199 facilities (6,000 beds) at the moment. We continue asking important facilities to become members via Future Planning Committee. It is globally recognized that for patients it is scientific to conduct clinical research by sharing information with scientific society and this also leads to visualization. Because a scientific society does not possess infrastructure or cannot perform clinical research, JGOG will be in charge of them. As we have already obtained approval of the Japan Society of Gynecologic Oncology (Chairperson: Nobuo Yaegashi), we would be able to enjoy an advantage in obtaining external funds, such as from AMED and the Japan Medical Association, if we can plan significant researches by using the system. Toward standard medical care in Japan and Asia, JGOG will develop a system for Japan and Korea to take the leadership or act as the coordinator by using our experiences in international trials. We exchanged an agreement with KGOG. Actually, several shared researches are already ongoing. Taiwan has also mentioned its intention of joining. A research system that includes also other regions of Asia has come in sight of actualization. TRI, which has a network in Asia, will play a key role. Also AGOG will make a fresh start under Professor Ochiai. It is now rooming in JGOG, but it will manifest its role as an independent receptacle of Asia under the leadership of Professor Ochiai. We will also promote linkage with Europe and America in a form that does not overlap with NRG-Japan, and I'd like to ask GCIG members to be further active.

Reformation that aims at becoming an approved NPO in several years will start this year, which is a year of director election. By becoming an approved NPO, we will be able to substantially receive as much contributions as a public service corporation, which will lead to development of nonprofit business. About 10 persons are acting as directors in both JGOG and JSGO. As we have to reduce the number, we have asked institute tops who are JSGO directors to allow their direct subordinates to act as directors of JGOG. Needless to say, the representative of the institute remains to be the institute top.

I appreciate your ongoing support and cooperation to JGOG.

JGOG's activities



Report of the 14th Annual Meeting of JGOG

Daisuke Aoki, M.D., Ph.D.

Vice President, JGOG

The Japanese Gynecologic Oncology Group (JGOG) held its 14th annual meeting on December 4th, 2015 in Kokuyo Hall (Shinagawa, Tokyo). Professor Toru Sugiyama, newly elected president of JGOG, delivered the opening address.

In the morning reports from several committees were presented. The educational committee explained the rationale for various new clinical trials proposed by junior doctors. The current state of international clinical trials was then presented (GCIG, AGOG, GOG-Japan, etc.), and future plans for these trials were discussed. The highlight

of the morning sessions, however, was the invited lecture by Professor Byoung-Gie Kim, President of the Korean Gynecologic Oncology Group (KGOG). Professor Kim described current KGOG activities and reported on several current clinical trials and how they plan to develop them in the future. He also discussed some promising potential Japan-Korea collaborations.

The accounts for 2015 were ratified and the budget statements for 2016 were approved by the General Assembly. Business reports for 2015 and plans for 2016 were also approved. Financial resources in 2015 were still limited, but the situation is gradually being improved.

In the afternoon current JGOG clinical trials were reviewed and their progress was reported. New clinical tri-

als, and plans for future clinical trials, on a range of gynecologic malignancies were also discussed. An open discussion was then held on these new ideas and trial concepts.

At the end of the annual meeting, Dr. Yasuhiro Fujiwara, Director-General of the Strategic Planning Bureau at the National Cancer Center, Japan, gave a lecture updating us on current research ethics entitled "Ethical Guidelines for Medical and Health Research Involving Human Subjects." These guidelines were revised in March 2015.

Despite a tight schedule the meeting progressed smoothly with nearly three hundred doctors from all over the country in attendance. The annual meeting was brought to its conclusion by my closing remarks.

JGOG's activities



Report of the 1st KGOG-JGOG collaboration meeting

Kimio Ushijima, M.D., Ph.D. Chair of the Committee of Japan-Korea, JGOG

JGOG and KGOG have had 11 joint meetings during conferences held in Japan or Korea. During a series of meetings, a tendency has grown toward conducting collaboration studies using a common protocol in order to compete against large-scale studies in Europe and America. When Dr. Byoung-Gie Kim, president of KGOG, visited the general meeting of JGOG held in Japan last year, he

proposed having concrete discussion during the KGOG meeting in spring 2016. On April 8, 2016, the first KGOG-JGOG collaboration meeting was held at Heunde Grand Hotel in Busan; and Vice-President Enomoto and Directors Kigawa, Okamoto, and Ushijima attended the meeting representing JGOG.



In the meeting, present states of data centers and biobanks of JGOG and KGOG were reported. In both Japan and Korea, superb electronic registration systems that can even record CRF are already operating. As candidates of joint clinical tests, JGOC named JGOG2047 and JGOG3020, and KGOG mentioned KGOG3033, which is on postoperative therapy of malignant germ cell tumor. Their feasibility was discussed, and need of checking details was revealed. JGOG1077S had already been discussed in Korea and been conducted under an original KGOG study number. It was also decided to use the biobank in their own country because it is difficult to bring frozen specimen outside each country. During the

meeting, differences in clinical test environment between the countries became apparent. In Korea, patients are not required to pay any even in a voluntary test, but the researcher side pays everything. Professor Kim proposed investigating a new test that targets not a rare tumor but a frequent tumor in Asia in order to appeal to the world.

Finally, Professor Kim and Professor Enomoto signed an agreement, commemorative photos were taken, and the meeting was closed. The next meeting was decided to be held during the gynecologic oncology meeting in Yonago, to which persons engaged in data centers will be summoned to discuss concrete details.

JGOG's topics

Contribution of the Tohoku Medical Megabank Organization to tumor genome studies.

Naoko Minegishi, MD., Ph.D.
Tohoku University School of Medicine



Ethnic differences in genomic data require tumor genome studies in Japan to include a considerable number of control data and/or biospecimens from Japanese individuals who have not suffered from major disease. Tohoku University Tohoku Medical Megabank Organization (ToMMo) provides biospecimens, health-information, and genomic data, including whole genome sequence (WGS) data, from participants in population cohort studies. Furthermore, ToMMo and the Japanese Gynecologic Oncology Group (JGOG) support and conduct prospective studies to elucidate associations between gynecological tumor risks and genetic or lifestyle factors.

The ToMMo and TMM biobank

The Tohoku Medical Megabank (TMM) project is being conducted by ToMMo at Tohoku University and the Iwate Tohoku Medical Megabank Organization (IMM) at Iwate Medical University. The TMM project is part of the reconstruction effort after the Great East Japan Earthquake in 2011, and contains two large-scale population cohort studies and intensive human genome analyses¹⁾.

At the TMM biobank, located on the campus of ToMMo, we receive blood and urine samples collected in cohort studies of TMM projects and process these biospecimens using automated liquid handling systems after donor de-identification. These biospecimens are stored in fully automatic storage systems (-80°C and +4°C) and/or vapor-phase liquid

nitrogen systems. In addition, the DNA extraction procedures are fully automated. At each step of the procedure, ID uniqueness and time points are verified and recorded in our laboratory information management systems²⁾. These systems enable the TMM biobank to achieve a error rate (<0.4%) that is lower than that of other biobanks (0.8–1.0%). The TMM biobank has held ISO9001 (quality management system) certification since 2015 and ISO27001 (information security management system) certification since 2016. More than 5.8 million specimens can be stored in the TMM biobank. As of December 2016, 46% of the biobank storage capacity is filled with biospecimens obtained from nearly 150,000 1st stage participants of TMM cohort studies. The cohort and genomics data are stored in supercomputer systems at ToMMo (total nodes, 800; total memory, 111 TB; total storage, 18 PB).

Genomics studies and data management in ToMMo

We have conducted WGS analyses of genomic DNA from participants in these cohort studies using next-generation sequencers (Hiseq2500, PacBio RSII, and others). The allele frequency data for 28,000,000 autosomal single nucleotide variations (SNVs) obtained from more than 2000 individuals³⁾ and the results of long-read genome analysis are now available at our website (<https://ijgvd.megabank.tohoku.ac.jp>, <https://jrg.megabank.tohoku.ac.jp>). Based on these results, we have produced DNA array systems containing the minimal number of SNVs probes suitable for determining

SNVs and analyzing WGS data of the Japanese population. We also perform metabolome and proteome analyses⁴⁾, and statistical analyses of these data can be accessed at our website (<https://jmorp.megabank.tohoku.ac.jp>).

Individual genomic and cohort data of de-identified participants are available from the TMM biobank after approval by the Institutional Review Board and TMM Sample and Data Access Committee.

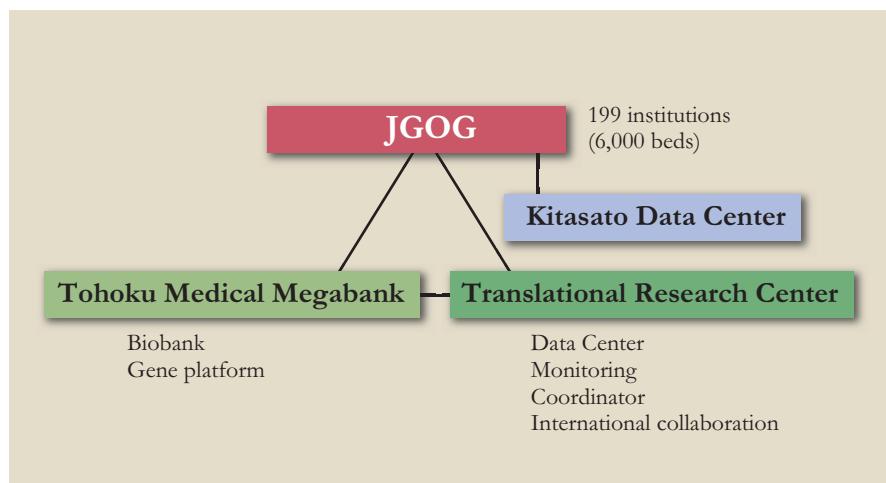
ToMMo and JGOG

We can provide our cohort data and share expertise on the biobanking procedures with the JGOG study group. After fol-

low-up studies, ToMMo and JGOG will clarify the genetic and environmental risks associated with gynecological cancers.

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JGOG's topics

JGOG2047: A multicenter phase II/III clinical trial comparing dose-dense paclitaxel plus carboplatin and conventional triweekly paclitaxel plus carboplatin for patients with stage I-IV and recurrent uterine carcinosarcoma

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Uterine carcinosarcomas (UCS), also known as malignant mixed mullerian tumors (MMMTs), are rare neoplasms of the uterus. They account for 2-5% of all uterine cancers, with an estimated annual incidence of less than two per 100,000 women. UCS is an aggressive uterine cancer with poor survival rates, even when presenting at an early stage. Previous studies have estimated that median overall survival is approximately 21 months, and less than 1 year in advanced or recurrent disease. More than 40% of women with UCS have advanced-stage disease, and more than 50% of these tumors will recur. Histologically, UCS displays both epithelial and sarcomatous differentiation. Recent genetic analyses suggest that most UCS are monoclonal in origin, and they are

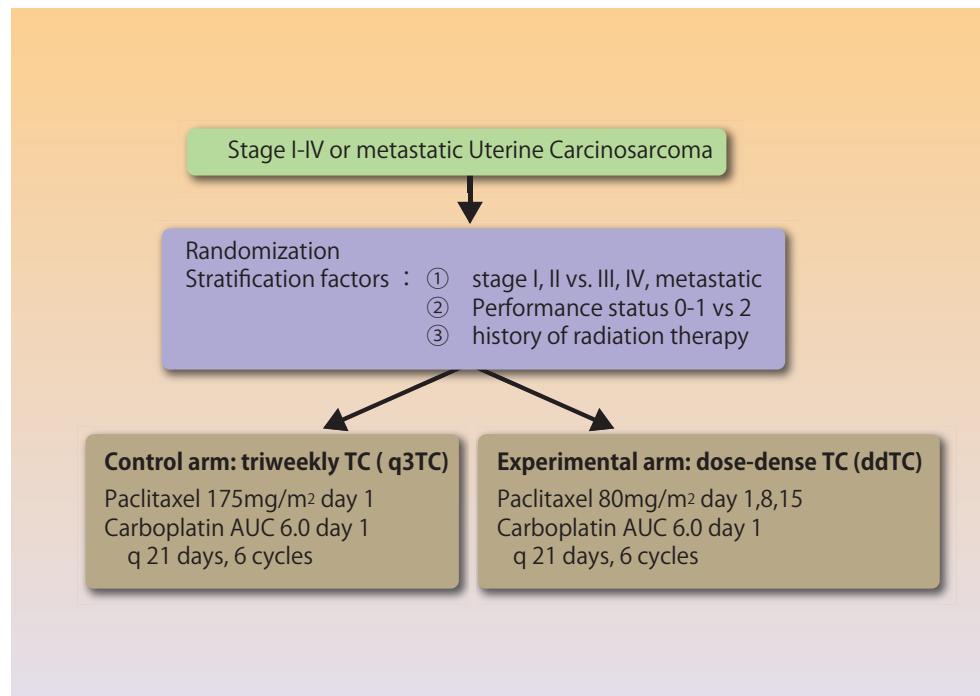
currently classified as metaplastic carcinomas. Clinically, the behavior of UCS is more similar to carcinomas than to the sarcomas in terms of dissemination and sensitivity to platinum-based chemotherapy.

Surgery is the cornerstone of treatment for UCS. The high rate of recurrence underlines the need for effective adjuvant treatment. To date ifosfamide-based combination chemotherapy (paclitaxel or cisplatin) has been the standard chemotherapy. However, growing evidence suggests that combination therapy with paclitaxel and carboplatin (TC) is promising. A phase II trial (GOG232B) has shown that the combination of triweekly administration of carboplatin and paclitaxel resulted in a high response rate of 54% and median

progression-free survival of 7.6 months. A Gynecologic Oncology Group (GOG) phase III trial (GOG261) comparing TC with ifosfamide plus paclitaxel is currently ongoing. It is anticipated that TC will be a new standard treatment for patients with UCS. The Japanese Gynecologic Oncology Group (JGOG) reports that dose-dense paclitaxel in combination with carboplatin improves disease-free survival and overall survival compared to conventional triweekly TC chemotherapy in patients with stage II-IV ovarian cancer (JGOG3016). The dose-dense design is also an attractive

treatment strategy for other gynecological malignancies that utilize paclitaxel and carboplatin. It is hypothesized that the dose-dense paclitaxel and carboplatin design can improve survival outcome in patients with UCS and we intend to conduct a phase II/III study to test this hypothesis.

The aim of the study is to assess the efficacy of dose-dense paclitaxel and carboplatin compared to conventional triweekly TC chemotherapy in patients with chemotherapy-naïve stage I-IV and metastatic UCS. We will open the trial early in 2017 and welcome enquiries from patients with UCS.



JGOG2047 Schema

Editorial postscript



We are happy to send you "JGOG International No.11". JGOG was launched in 2002 as a non-profit organization; and after its history of 14 years, it is facing the time of innovation and reformation. Aiming at further development, JGOG decided to promote translational research under the leadership of President Toru Sugiyama by enhancing linkage with Tohoku Medical Megabank Organization University (ToMMo). Tohoku Medical Megabank Organization University (ToMMo) is featured in this newsletter as JGOG's topic. There is another topic featured, which is on JGOG2017: adjuvant chemotherapy for uterine sarcoma by dose-dense cytotoxic chemotherapy and conventional cytotoxic chemotherapy and information about randomized phase II/III design for comparative clinical trials as chemotherapy for recurrent cancer. The test is the latest JGOG's clinical trial for endometrial cancer. The newsletter also carries a report on the 1st KGOG-JGOG Collaboration Meeting, which was held last year with KGOG, which has been our most reliable partner since the establishment of JGOG. We'd be very happy if the strengthened linkage with KGOG would help JGOG, together with KGOG, to plan and execute high-quality clinical research that can be dispatched not only to Asia but also to the entire world.

In 2016, the Olympics were successfully held in Rio de Janeiro, Brazil. Japan is gradually livening up toward the Tokyo Olympics, which will be held in 4 years. Enthusiasm is rising also in JGOG toward further globalization by organizational reformation.

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