The History and Future of the Urologic Oncology Study Group (UOSG) of the Japan Clinical Oncology Group (JCOG)

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The Urologic Oncology Study Group (UOSG) of the Japan Clinical Oncology Group was founded in 2001. At the beginning, 41 collaborative institutions participated, and the first group representative was Kenichi Tobisu, from the Shizuoka Cancer Center. In the last 10 years, three JCOG studies have been conducted. In two of them, patient registration has been closed and they are now in the follow-up period. The third study has just started registration in 2011. At present, we have not yet completed the final data analyses in any of the studies. In the meantime, however, we have performed a few retrospective analyses by collecting clinical data from each of the participating institutions, and the results were published as important Japanese data. All the activities of the investigation were supported by the Health and Labor Sciences Research Grants for Clinical Research in Japan. The UOSG encountered great difficulties in planning the prospective study, completing the sophisticated protocol and recruiting the expected number of patients. It usually took a longer time than expected to achieve the final goal. This was probably due to insufficient experience in conducting sophisticated protocol studies and immaturity in managing a study group. Now, the UOSG consists of 38 institutions and is gradually overcoming these problems. In 2011, the UOSG changed its group representative to Yoshiyuki Kakehi from Kagawa University and continues to strive to meet the challenge of becoming a more active group. In this review, we provide an overview of the history and achievements of the UOSG over the past 10 years, along with a list of participating institutions.

Key words: Urologic Oncology Study Group – Japan Clinical Oncology Group – bladder cancer – prostate cancer – upper urinary tract urothelial cancer

OVERVIEW OF THE HISTORY OF THE UOSG

The Urologic Oncology Study Group (UOSG) of the Japan Clinical Oncology Group (JCOG) was founded in 2001. In urological practice, the most frequently treated malignant disease is prostate, bladder and kidney cancer. However, even in each major institution, the volume of these patients is not very high. Therefore, many institutions must participate in a single clinical study so that an adequate number of eligible patients are registered. Furthermore, the researchers in various local study groups were not trained enough to conduct the sophisticated prospective study. In these circumstances, the USOG was established to solve and overcome these problems. The first multi-institutional prospective randomized study conducted by the group was JCOG 0209, which evaluated the survival benefit of two cycles of neoadjuvant MVAC (methotrexate, vinblastine, Adriamycin and cisplatin) chemotherapy for T2-4aN0M0 invasive bladder cancer. Taiji Tsukamoto, a professor at Sapporo Medical
University, was a principal investigator and was supported by the Health and Labor Sciences Research Grants for Clinical Research (2001–07). JCOG 0209 started patient registration in 2003, but could not complete the expected enrollment and closed in 2009 when 130 patients had registered. These registered patients will be followed up until 2014.

The second study was JCOG 0401, which compared anti-androgen monotherapy with external beam radiation therapy (EBRT) for patients with biochemical failure after radical prostatectomy. The principal investigator was Seiji Naito, a professor at Kyusyu University. This study was supported by radiotherapists of each institution and the Health and Labor Sciences Research Grants for Clinical Research (2003–10). JCOG 0401 started patient registration in 2004 and completed the enrollment in 2011. The 210 registered patients will be followed up until 2016.

The third study, JCOG 1019, which aimed to develop the appropriate treatment strategy for ‘high-grade T1 bladder cancer’ after the second transurethral resection (TUR), was approved by the JCOG protocol committee and prepared for recruiting patients in 2011. The principal investigator was Taiji Tsukamoto, a professor at Sapporo Medical University. This study will be supported by three pathologists for central pathological diagnosis and has been supported by the Health and Labor Sciences Research Grants for Clinical Research since 2010.

In 2011, we prepared the retrospective study on upper urinary tract urothelial cancer (UUTUC) (JCOG 1110-A) that will provide an important supporting date to the next prospective randomized study.

At present, 38 collaborative institutions are participating as active members of the UOSG. Thirty of them are University hospitals and seven are cancer centers that specialize in cancer treatment. In the last 10 years, the UOSG has experienced serious delay in completing the planned patient recruitment. This was due to several factors, such as a lack of experience in conducting sophisticated prospective studies, a small number of eligible patients in each participating institution and so on. In 2011, Yoshiyuki Kakehi from Kagawa University became the group representative, and the UOSG continues to strive to meet the challenge of becoming a more active clinical study group.

OUTLINE AND PRESENT STATE OF EACH STUDY

JCOG 0209

The standard treatment for T2-4aN0M0 bladder cancer is total cystectomy with urinary tract reconstruction. However, reported 5-year overall survival was $\sim 65–75\%$ for pT2 and $50–65\%$ for pT3 (1). The same outcome was summarized by our group in Japanese cases (2). Until 2000, various kinds of adjuvant and/or neoadjuvant treatment such as radiation or systemic chemotherapy had been tested. However, none of them had been recognized as an established standard option.

On the other hand, since 1985, systemic MVAC chemotherapy has been recognized as a standard treatment that can be expected to provide significant survival benefits (3). In 2001, SWOG reported the results of a prospective randomized study, evaluating the efficacy of neoadjuvant MVAC chemotherapy before radical cystectomy (4). It was reported that three cycles of neoadjuvant MVAC plus total cystectomy may realize more promising 5-year overall survival compared with cystectomy alone. However, it was not accepted as a global standard at that time, including in Japan. We are also concerned that Japanese patients may not be able to endure three cycles of neoadjuvant MVAC plus radical cystectomy.

Therefore, we conducted the prospective randomized study, JCOG 0209, comparing two cycles of neoadjuvant MAC plus cystectomy with cystectomy alone. The study started patient registration in 2003, aiming at completing the enrollment of 260 patients in 3 years. However, it could not be accomplished within the planned period. Finally, registration was closed in March 2009, after recruiting 130 patients who completed the protocol treatment and will be followed up until 2014.

When the protocol concept was discussed, we investigated the total number of cystectomy cases and final outcomes in each participating institution to consider the feasibility of this study. And we finally planned to enroll 260 patients in 3 years. However, when precise eligibility criteria were applied, eligible patients were less than half of the total cystectomy patients in each institution. Furthermore, in the twentieth century, patients with invasive bladder cancer have continually decreased in each institution. Thus, we encountered great difficulties in recruiting patients.

Though the initially planned registration could not be attained, this is the first experience for Japanese urologists of 130 patients with invasive bladder cancer being recruited in the sophisticated prospective randomized study conducted in Japan. The monitoring report shows that two cycles of MVAC chemotherapy can be well tolerated in Japanese patients and does not deteriorate the total treatment schedules. The final conclusion regarding the efficacy of neoadjuvant MVAC before cystectomy is awaited. It may be difficult to draw a definite conclusion about the survival benefits of neoadjuvant MVAC plus cystectomy against cystectomy alone, but it may offer some suggestions about who will benefit by neoadjuvant chemotherapy.

JCOG 0401

Since 1990, the prostate-specific antigen (PSA) test has gradually become popular in Japan, and the incidence of organ-confined prostate cancer has been rising. The standard treatment for early prostate cancer with 10-year or longer life expectancy is radical prostatectomy. After radical prostatectomy, $\sim 20–30\%$ of the patients will develop PSA failure...
(5,6). In Japan, for patients with PSA failure, hormonal therapy has been a predominantly selected treatment. However, in the 1990s, salvage radiation therapy gradually became popular in leading hospitals. Thus, which will be beneficial or what is an appropriate treatment selection criterion for Japanese patients became important clinical questions.

To answer these questions, JCOG 0410, which compares these two modalities, was conducted. Patients whose PSA level was below 0.1 ng/ml after prostatectomy and showing an increase of more than 0.4 ng/ml were randomized in two groups. One was treated with bicalutamide and the other was treated with EBRT. When PSA showed an increase of higher than 0.4 ng/ml, it was defined as a failure of the treatment. In the former group, when bicalutamide treatment failure was diagnosed, the luteinizing hormone-releasing hormone (LHRH) analog was adopted as a second-line hormonal therapy. In the latter group, when PSA became higher than 0.4 ng/ml, bicalutamide was commenced, and thereafter, once resistance to bicalutamide was shown, LHRH analog was administered. The primary endpoint was time to the treatment failure for the LHRH analog from randomization. The study commenced registration in 2004 and closed in May 2011, after enrolling 210 patients. At present, protocol treatment is being continued in both arms and patients will be followed up until 2016.

**JCOG 1019**

The standard treatment for non-muscle invasive bladder cancer (Ta, T1) is TUR of the bladder tumor (TURBT). After TURBT, prophylactic bladder instillation therapy, such as mitomycin C, Adriamycin or Bacillus Calmette-Guerin (BCG), is applied according to the evaluated risk of recurrence and progression (7,8). In the case of high-grade cancer, especially in T1 cancer, secondary TUR after primary TURBT is recommended as a standard treatment. Then, irrespective of the pathological state of the secondary TUR, BCG bladder instillation therapy is recommended in the present clinical guidelines (7,8). However, ‘high-grade, T1 bladder cancer’ is considered to be a heterogeneous patient group. Some showed rapid recurrence and progression, but some have a longer tumor-free period after initial TURBT. In the latter cases, urgent BCG instillation therapy will be an unnecessary overtreatment in terms of quality of life and the risk of adverse reaction to the BCG instillation.

In JCOG 1019, patients with ‘high-grade T1 bladder cancer’ were registered, and a second TUR was performed in all cases. In the literature, it is reported that after the second TUR, approximately half of the patients had residual UC (9). The other half of the patients were proved to be T0. These patients with T0 after the second TUR were re-registered and randomized into two groups. The standard group was treated by prophylactic BCG instillation, and the test group was just followed up without instillation therapy. The primary endpoint was the time duration until patient showed cancer recurrence with T1N0M0 or a more advanced stage.

At present, the full protocol has just been approved by the JCOG protocol committee, and enrollment has commenced. The planned time duration for patient recruiting is 4 years, and after a 2-year follow-up, the results will be analyzed.

**Retrospective Study of UUTUC JCOG1110-A**

The standard treatment for UUTUC without metastasis is nephroureterectomy with a cuff of the bladder plus regional lymphadenectomy (LA) for high-grade tumors (7,8). At present, reliable criteria have not yet been established for the indication and range of the LA.

One more important problem in the treatment of UUTUC is a frequent recurrence of UC in the bladder after curative surgery (10). According to the literature, the recurrence rate in the bladder is reported to be as high as ~50%. Nevertheless, usually, almost all the urologists do not try prophylactic bladder treatment. Once bladder cancer is detected in the follow-up period, TURBT is the first step of the treatment, followed by various prophylactic bladder instillation therapies according to the risk stratification of recurrence and progression. As is often the case with primary bladder cancer, frequent recurrence after initial TURBT and progression in some of them are the characteristic problems. Therefore, it may be beneficial for the patients to start prophylactic bladder instillation therapy immediately after radical surgery. This is the second clinical question concerning UUTUC.

As mentioned above, one more clinical question is the significance of LA. If LA contributes to the cure rate, the next question is the criteria for selecting the patients who will be benefited by LA, and when LA is indicated, the range of LA according to the tumor site, estimated stage and grade of the tumor.

Before conducting a prospective randomized trial for offering suggestions for these clinical questions, the real situation regarding the clinical practice for UUTUC in Japan should be clarified. The following clinical information, such as the number of the patients treated, stage distribution, surgical mode, indication and range of LA, recurrence rate, site and time duration after surgery, treatment interventions after recurrence and final prognosis, will be collected from all participating institutions. This retrospective study, JCOG2011110-A, will be performed with the support of the JCOG Data Center.

**Specific Problems in UOSG**

The most difficult problem the UOSG encountered in the last 10 years was the slow pace of patient registration. In JCOG 0209, the study closed before the planned number of patients was registered. In JCOG 0401, it took 7 years to complete the recruiting, which was a 3-year delay from the
initial problem. Concerning this problem, several factors can be speculated.

In Japan, the most frequently treated urological cancer is prostate cancer, followed by bladder cancer, and renal cell carcinoma. However, the volume of newly diagnosed patients in each institution is small, and if the eligibility criteria of the study are applied, the number of eligible patients decreases much more. Therefore, for recruiting a sufficient number of patients to accomplish one prospective study, many institutions must agree with the protocol and participate in the study. However, it is not so easy to agree on many points in the details when discussing about a single protocol. Precisely speaking, each participating institution has its own way of thinking about indications for various treatment options, operative procedures or chemotherapeutic regimens. This is one reason why it took a longer time to complete one full protocol.

Leading medical institutions in practically every district of Japan are university hospitals. They not only have their own style and history of clinical practice, such as different modes of surgery or different treatment strategies, but also have their own study group consisting of several university hospitals and their referring hospitals. They have been conducting independent studies, in which the eligibility criteria sometimes overlapped with those of the JCOG study. In such cases, eligible patients had to be allocated for several independent studies. This caused the delay in recruiting patients, because, as mentioned above, the eligible patients were originally limited in number.

One more problem was that it took a longer time, e.g. more than 2 years, to complete the full protocol, probably due to lack of experience in composing a well-considered and polished protocol. Thus, more than 2 years had passed since the approval of the study concept until the beginning of registration. In the meantime, many investigators lost the motivation for completing the study. Finally, it took 10 years until the UOSG learned enough for preparing and conducting the sophisticated protocol study.

**FUTURE PERSPECTIVES OF THE UOSG**

If Japanese urologists intend to produce clinically significant evidence that can appeal to the world, many major institutions must cooperate together and collaborate with a reliable data management center. From this point of view, the UOSG must be one of the most promising study groups in Japan, because it consists of major Japanese institutions in terms of experiences and quality in urologic oncology and is supported by the established JCOG Data Center. Even now, we are expected to contribute in developing and verifying the new treatment option for urologic cancer.

The UOSG has come a long way in establishing a harmonized group that can share the clinical questions and the same clinical activity style after heated discussions. The above-mentioned problems will be gradually solved. Experiencing successful completion of the studies that will influence clinical activity worldwide, we will gradually realize the significance and pleasure of multi-institutional collaboration.

As a practical strategy, for maintaining the motivation of the participating institutions, we should conduct various small retrospective and prospective studies independent from the JCOG Data Center. Speed in completing the protocol and attaining expected enrollment will be the indispensable factor for the future progress of the UOSG.

**PARTICIPATING INSTITUTIONS (AS OF 31 OCTOBER 2011)**

Hokkaido University, Sapporo Medical University, Hiroasaki University, Tohoku University, Akita University, Yamagata University, Miyagi Cancer Center, Tochigi Cancer Center, University of Tsukuba, Chiba University, Keio University, National Defense Medical College, The Jikei University, Teikyo University, National Cancer Center Hospital, Kitasato University, Niigata Cancer Center, Niigata University, University of Yamanashi, Shinsyu University, Shizuoka Cancer Center, Hamamatsu University, Nagoya University, Mie University, Nara Medical University, Kyoto University, Osaka Medical Center for Cancer and Cardiovascular Disease, Kobe University, Tottori University, Kagawa University, Shikoku Cancer Center, Shimane University, Yamaguchi University, Kyushu University, Harasanshin Hospital, Kumamoto University, Kurume University and Kagoshima University.

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**Conflict of interest statement**

None declared.

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