A randomized controlled trial has started in Japan to evaluate radiotherapy and endocrine therapy for prostate-specific antigen (PSA) failure after radical prostatectomy. Patients who have PSA failure after radical prostatectomy for localized prostate cancer (T1–2N0M0) are randomized into treatment groups of either radiotherapy ± endocrine therapy or endocrine therapy alone. The Urologic Oncology Study Group (UOSG) in the Japan Clinical Oncology Group (JCOG) composed of 36 specialized institutions will recruit 200 patients. The primary end-point is time to treatment failure (TTF) of bicalutamide, and secondary end-points are TTF of protocol treatment, progression-free survival, overall survival, adverse events and quality of life (QOL). The Clinical Trial Review Committee of the JCOG approved the protocol on April 13, 2004, and the study was activated on May 17, 2004.

Key words: prostate cancer – prostatectomy – PSA failure – endocrine therapy – radiation
randomized trials. However, the 10 year overall survival rate is expected to be >80% in this study, therefore OS will not be a good candidate for the primary end-point. The clinical progression-free survival is also not adequate as the primary end-point for the same reason. Regarding ‘PSA failure’, it may be a potential candidate for the primary end-point, but PSA failure will occur at least three times more frequently in the experimental arm, which causes confusion in evaluation. Therefore, the adequate primary end-point would be time to treatment failure (TTF) of luteinizing hormone-releasing hormone (LH-RH) analog as a hormone-refractory state of prostate cancer. As the TTF of bicalutamide can be evaluated more quickly than that of LH-RH analog and thus should be its good surrogate end-point, the TTF of bicalutamide is selected as a primary end-point in this study. In summary, the primary end-point is the TTF of bicalutamide, and secondary end-points are TTF of protocol treatment, clinical progression-free survival, OS, adverse events and patient-reported quality of life (QOL).

ELIGIBILITY CRITERIA

Tumors are staged according to the General Rule for Clinical and Pathological Studies on Prostate Cancer (Japanese Urological Association, The Japanese Society of Pathology), which is the 1997 revision of the TNM Classification of Malignant Tumours by the International Union Against Cancer (UICC) (3).

INCLUSION CRITERIA

(i) A diagnosis of localized prostate cancer (clinical stage T1–2N0M0) which was treated by radical prostatectomy; (ii) pathological stage: pT0/2/3 and pN0/x; (iii) the serum level of PSA once it has reached <0.1 ng/ml after radical prostatectomy and then increased to ≥0.4 ng/ml; (iv) a serum level of PSA ≤1.0 ng/ml at study entry; (v) no clinical recurrence based on abdominal and pelvic CT, and a bone scan; (vi) no history of chemotherapy, radiation therapy or endocrine therapy for any cancer; (vii) age ≥20 and ≤79 years; (viii) an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (ix) no blood transfusion within 28 days of entry; (x) sufficient organ function within 28 days of entry; and (xi) written informed consent.

EXCLUSION CRITERIA

(i) Synchronous or metachronous (within 5 years) malignancy other than carcinoma in situ; (ii) mental disease or mental symptoms which would affect the participant’s decision to participate; (iii) continuous medication of steroids (exclude external use of steroids for skin); (iv) ischemic heart disease or arrhythmia which needs medical treatment; (v) poorly controlled hypertension; (vi) poorly controlled diabetes mellitus; (vii) history of cerebral infarction or myocardial infarction within 6 months; (viii) liver cirrhosis; and (ix) interstitial pneumonia which requires ventilation assistance, oxygen inhalation, steroids or diuretic medicine.

RANDOMIZATION

Using telephone or fax contact with the JCOG Data Center after confirmation of the above criteria, patients are randomized by the minimization method of balancing the groups according to the Gleason score of the radical prostatectomy specimen, period from operation to PSA failure, and institution.

TREATMENT METHODS

Endocrine therapy alone group (standard arm). The protocol treatment includes the bicalutamide medication (80 mg/day). After TTF of bicalutamide, it is followed by LH-RH analog (leuprolin acetate 3.75 mg/4 weeks or 11.25 mg/12 weeks, goserelin acetate 3.6 mg/4 weeks or 10.8 mg/12 weeks).

Radiotherapy ± endocrine therapy group (experimental arm). The total dose of 64.8 Gy/36 Fr (50 days) external beam irradiation is delivered to the prostatic bed. If the patient has no treatment failure, no additional therapy will be given. In case of treatment failure of radiation therapy, bicalutamide medication will be started in the same way as in the standard arm. After the treatment failure of bicalutamide, a LH-RH analog is given to the patients as in the case of endocrine therapy alone.

DEFINITION OF TREATMENT FAILURE

(i) PSA increase beyond 0.4 ng/ml if previous value is <0.4 ng/ml (ii) Any PSA increase if previous value is ≤0.4 ng/ml (iii) Clinical progression or clinical recurrence (iv) Adverse event (v) Patient refusal to continue treatment (vi) Any cause of death (vii) Poor compliance (less than two-thirds of planned dose) of oral bicalutamide at two consecutive visits (only for bicalutamide treatment failure)

FOLLOW-UP

All patients are followed-up by their urologist at least every 3 months for more than 5 years. Blood tests including PSA and urinalysis are performed during the follow-up interval. Abdominal and pelvic CT, chest X-ray and bone scan are carried out every 12 months. The symptoms and adverse events are surveyed at each visit.

STUDY DESIGN AND STATISTICAL METHODS

This trial is designed to evaluate the superiority of radiotherapy ± endocrine therapy to endocrine therapy alone in terms of the TTF. Almost half of the patients can be cured by radiation therapy alone (4–6), therefore, these patients are
expected to have a greatly prolonged TTF after radiation (radiation responder). In contrast, the other half of the patients irradiated are expected to have a treatment failure of radiation therapy (non-responder) and they will have a TTF not significantly shorter than that of those on bicalutamide therapy. In the standard arm, there have been no published data concerning the TTF of bicalutamide for PSA failure after radical prostatectomy. Therefore, we assumed the TTF of bicalutamide therapy in this study to be 4–5 years, based on the report in which the median TTF of bicalutamide therapy for localized prostate cancer was 63.5 months (7). The median TTF in the experimental arm can be calculated on the assumption that the TTF in a radiation responder (50% of the experimental arm) is prolonged three times more than in the non-radiation responders (50% of the experimental arm). Therefore, the median TTF in the experimental arm will be 6.6 years (4.0 years in non-responders and 12.0 years in responders) and 8.3 years (5.0 years in non-responders and 15.0 years in responders). We calculated sample sizes based on Shoenfeld and Richter’s methods (8) with 5 year follow-up after 4 years of accrual. If the TTF in the standard arm is 4.0 years, the detectable difference in TTF and sample size per arm will be 2.6 years and 83 cases, respectively. If TTF in the standard arm is 5.0 years, the detectable difference in TTF and sample size per arm will be 3.3 years and 93 cases, respectively. This will provide an 80% power to detect the difference between the assumed TTF in the experimental arm and the TTF in the standard arm (non-responder in the experimental arm compatible) at a 5% one-sided alpha level. Based on these data, the planned sample size is 100 cases in one arm.

QOL

All the patients are enrolled prospectively in a QOL survey using a validated assessment tool and are evaluated before the treatment and 1-year after the treatment. The health-related QOL is assessed using the Japanese version of the RAND Health-Item Short Form 36 (SF-36) version 2.0 (9), and cause-specific QOL is analyzed by the UCLA Prostate Cancer Index which was established by Litwin et al. (10). The Japanese version of SF-36 and that of UCLA PCI were assessed as described previously (11–13).

INTERIM ANALYSIS AND MONITORING

An interim analysis is planned to be performed once, taking into account multiplicity using the Lan and DeMets approach. The Data and Safety Monitoring Committee (DSMC) of the JCOG independently reviews the interim analysis report, and an early termination of the trial may be considered at that stage. In-house interim monitoring is performed by the Data Center to ensure data submission, patient eligibility, protocol compliance, safety and on-schedule study progress. The monitoring reports are submitted to and reviewed by the UOSG and the DSMC every 6 months.

PARTICIPATING INSTITUTIONS (FROM NORTH TO SOUTH)

Hokkaido University, Sapporo Medical University, Tohoku University, Miyagi Cancer Center, Akita University, Tsukuba University, Tochigi Cancer Center, Gunma University, Chiba Cancer Center, Chiba University, National Cancer Center Hospital, Tokyo Women’s Medical School, Keio University, The Jikei University, Nippon Medical School, Kitasato University, Niigata Cancer Center Hospital, Niigata University, Yamashashi University, Shinsu University, Hamamatsu Medical School, Shizuoka Cancer Center, Nagoya University, Mie University, Kyoto University, Osaka Medical Center for Cancer and Cardiovascular Diseases, Kobe University, Nara Medical University, Shimane University, Kurashiki Central Hospital, Okayama University, Kagawa University, National Shikoku Cancer Center, Kyushu University, Kurume University and Kagoshima University.

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References