using number of metastases, primary site, abdominal mass and lung metastasis as risk factors for patients with a poor prognosis from IGCCCG database. This tree classified five subgroups that differed in terms of 2-year survival ranging from 38% to 73%.

In summary, we investigated the survival of metastatic germ cell tumor patients treated between 1990 and 2001 in Japan based on the IGCC classification. Survival tended to increase for any risk group, and significantly increased among patients with a poor prognosis. This increase is most likely attributable to more effective chemotherapy regimens and more extensive care at institutions where staff had accumulated much experience with such patients. The IGCC classification is a useful criterion enabling to distinguish NSGCT patients according to prognosis. To target intensive treatment strategies for patients with a very poor prognosis, other prognostic factors must be identified that will detect the real stage of patients with a poor prognosis at the time of initial diagnosis.

Conflict of interest statement

None declared.

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Guidelines

Evidence-based Clinical Practice Guidelines for Prostate Cancer (Summary – JUA 2006 Edition)

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Working Group for Creation of Clinical Practice Guidelines for Prostate Cancer
The Japanese Urological Association
[Ministry of Health, Labour and Welfare (MHLW) Scientific Research Fund-Supported Project for Thorough Evaluation of Medical Technologies]

Introduction

The present Clinical Practice Guidelines for Prostate Cancer (GL) were created mainly by the Japanese Urological Association as part of the 2003–2004 Ministry of Health, Labour and Welfare (MHLW) Scientific Research Fund-supported Thorough Researches for the Evaluation of Medical Technologies. The guidelines are aimed to be used by general urologists and radiation oncologists committed to the treatment of prostate cancer. The complete text of these guidelines (a total of 233 pages) supervised by the Japanese Urological Association was already published in May 2006. The present edition is a summary of the complete text of the GL.

The working team for the creation of the present clinical practice guidelines involved Sadao Kamidono (Chairman of the Japanese Urological Association, Kobe University), who served as the team leader; Shinichi Ohshima (National Center for Geriatrics and Gerontology), who coordinated the overall structure of the GL; Yoshihiko Hirao (Nara Medical University), who collected Evidence-based Medicine (EBM)-intended reports; Kazuhiro Suzuki (Gunma University School of Medicine), who was responsible for the epidemiology section; Yoichi Arai (Tohoku University), who contributed to the diagnosis section; Hiroyuki Fujimoto (National Cancer Center), who contributed to the surgical treatment section; Shin Egawa (The Jikei University), who contributed to the radiation therapy section; Hideyuki Akaza (University of Tsukuba), who contributed to the pharmacotherapy section; and Isao Hara (Kobe University), who contributed to the expectant management and supportive care sections. Tomonori Hasegawa (Toho University) served as the advisor, and evaluated the GL using the Appraisal of Clinical Guidelines for Research and Evaluation (AGREE) Instrument. All of these contributors were committee members of the MHLW Scientific Research Fund-Supported project. Shiro Hinotsu (Tsukuba University) also joined the Working Group in the research of published reports and in creating the structured abstract and Yoshiyuki Kakehi (Kagawa University) joined the Working Groups in the field of expectant management and supportive care. Furthermore, researchers were assisted by 30 urologists affiliated with the Japanese Urological Association, four experts in public health and literature search, eight members of the Japanese Society for Therapeutic Radiation and Oncology and two members of the Japan Society of Clinical Oncology. A total of 317 urologists from 46 institutions all over Japan took part in the compilation of structured abstracts as directed by the Japanese Urological Association. Urologists outside the GL creation team contributed to the external evaluation of the first draft version of the GL. Thus, the present GL was completed in fact by the aggregated dedication of the Japanese Urological Association as well as the united efforts of the Japan Society of Clinical Oncology and the Japanese Society for Therapeutic Radiology and Oncology.

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EBM-intended practice guidelines

'Evidence-based Medicine' (EBM) has been defined as 'conscientious, accurate, careful utilization of optimal up-to-date information for making a medical decision for individual patients'. Practice guidelines have been defined as 'systematically developed statements concerning appropriate insurance-registered healthcare modalities for specific illness that can help the treating doctor and the patient making a medical decision'. However, no matter how far the information communication system has developed, it is difficult for healthcare providers, who are fully occupied with doing routine healthcare practices, to collect and read a huge volume of data in order to find out up-to-date optimal evidence. Therefore, there is a need for a systematically organized tool that helps the treating doctor as well as the patient making a medical decision. EBM is such a tool and practice guidelines are an aggregation of EBM for the treatment of specific diseases. EBM and practice guidelines may have to be revised according to changes in social and environmental circumstances along with the transition of time. The formulation of medical evidence is academic work, whereas the creation of practice guidelines is considered to be heavy-load labor. In the fields of medicine where one evolution is brought about after another, revisions needs to be made periodically to practice guidelines. Therefore, it is necessary to follow standardized processes when devising these guidelines.

The original draft of the present guidelines was made with reference to three guidelines that were prepared in the USA and Europe and have established evaluation, respectively. They are the Physicians Data Query (PDQ) Concerning Prostate Cancer issued by the National Cancer Institute (NCI), the guidelines prepared by the European Association of Urology (EAU), and the National Comprehensive Cancer Network (NCCN) devised by the American Cancer Society. Our team elucidated the present status of the diagnostic and treatment modalities for prostate cancer presented in these guidelines when they were created (1999).

Intending to incorporate findings obtained after 1999 and characteristics of prostate cancer in Japanese patients into the draft guidelines, clinical questions were raised for each specific subject and assumed clinical questions were set up in a standardized form. Clinical questions for the selection of relevant reports were selected. The selected clinical questions were reviewed and modified in order to improve the readability of the guidelines.

Eventually, 13 epidemiological clinical questions, 17 diagnostic clinical questions, 18 clinical questions concerning surgical treatment, 45 clinical questions concerning radiation therapy, 11 clinical questions related to pharmacotherapy, 6 clinical questions concerning expectant management and 4 clinical questions related to supportive care were selected.

To search the relevant reports that provided evidence for the draw answers (clinical answers), keywords were selected and a search formula was set up. The report search was limited to articles published after 1999, when the overseas reference guidelines were created. For the epidemiology section, clinical questions and keywords were set up that were separate from the American and European guidelines because this section was assumed to contain a large volume of statements inherent to Japan. For the search of the PubMed reports, the major topics of the Medical Subject Headings of the National Library of Medicine (MeSH) were used with reference to the selected keywords, and search formulae were devised. All of the search formulae have been described in the complete text to allow utilization in the case of future revision. Taking the work efficiency and future availability of journals into consideration, literature search was limited to a total of 26 journals, comprising 9 urological journals, 10 oncology journals, 3 journals for radiation therapy, and 4 general medical journals. A total of 4662 relevant reports were extracted, and 1033 articles that were considered by each subgroup to be important were selected. The selected articles were allotted to a total of 317 urologists at 46 nationwide institutions, who critically reviewed and edited each assigned article into an organized abstract of standardized form. These urologists flagged each prepared abstract with an evidence level rated according to the predefined criteria (Table 1). The evidence levels were summed up for an aggregation of information addressing each clinical question and each answer was prepared by assigning a recommendation class ranging from class A to class D. Class A recommendation indicates a best-recommended treatment or practice. Class B recommendation means a treatment or practice that is recommended in general. Class C recommendation represents a treatment or practice the value of which is equivocal due to a lack of adequate evidence. A Class D statement indicates a treatment or practice that should not be performed. All of the organized abstracts of the articles cited in the full text of the present guidelines were written on an electronic medium and have been attached as a CD-ROM to the Practice Guidelines for Prostate Cancer.

Despite the fact that the above-described compilation process was pursued when making up the present GL, some issues have evolved.

Table 1 Evidence levels (criteria of the Committee for the Clinical Practice Guidelines in Oncology)

I.	Evidence derived from a meta-analysis of multiple randomized controlled studies, or evidence from multiple randomized controlled studies.
II.	Evidence from at least one randomized controlled study, or evidence from multiple well-designed non-randomized controlled studies.
III.	Evidence from at least one well-designed semi-experimental research of other type, or evidence from well-designed non-experimental descriptive study such as comparative research, correlation research, and matched case-controlled study.
IV.	Report or opinion of expertise committee, or clinical experience of knowledgeable person.

Since these GL are mainly intended for use in Japan, studies on Japanese patients have been more closely searched and examined. However, most of the studies cited in these GL are studies performed overseas due to the levels of evidence. Thus, the present guidelines do not truly reflect the actual status of prostate cancer in Japanese patients. Regarding some subjects in the field of surgical treatment that are difficult to evaluate in randomized controlled studies, statements have been presented naturally with a low evidence level, or there is no study to obtain evidence. Recommendation classes as well as evidence levels presented in these guidelines were determined by the individual subgroups of our teams responsible for each section, based on global consideration of all the extracted evidence. Since it is difficult to determine an evidence level for statements in the field of epidemiology, statements in the epidemiology section are not flagged with any recommendation class. The Roman numeral in a parenthesis at the tail of the reference number denotes an evidence level as defined in Table 1.

A. Epidemiology

1. Morbidity and mortality

Prostate cancer predominantly affects elderly men, compared with other cancer species. The global age-adjusted morbidity rate of prostate cancer (age-adjusted morbidity rate : percentage of patients per 100 000 men per year) is 19.8, which stands as the third highest following 37.5 for lung cancer and 24.5 for gastric cancer. The morbidity of prostate cancer greatly varies across regions in the world. The morbidities of prostate cancer in advanced countries are generally more than three times as high as those in developing countries. In Japan, the age-adjusted morbidity of prostate cancer in men (based on the 1985 population) is 19.9, which is the sixth highest following those of gastric cancer, lung cancer, colon cancer, hepatic cancer and rectal cancer. However, it is forecast that the incidence of prostate cancer will become the second most prevalent following lung cancer by 2020 in Japan.[1,2]

The global age-adjusted mortality rate of prostate cancer is 8.2, which is the fifth most prevalent following 33.7 for lung cancer, 19.1 for gastric cancer, 14.2 for hepatic cancer and 10.7 for colon/rectal cancer. In Japan, the 2001 age-adjusted mortality rate of prostate cancer in men is 8.4, which is the eighth highest following lung cancer, gastric cancer, hepatic cancer, colon cancer, pancreatic cancer, esophageal cancer and rectal cancer. The number of Japanese men dying of prostate cancer accounts for 4.2% of all Japanese men dying of any cancer.

2. Risk factors

Prostate cancer can be latent as it is sometimes detected incidentally by microscopic investigation of biopsy specimen collected during any interventional procedure. The incidence of latent prostate cancer increases along with the advancement of age. However, the incidence of latent prostate cancer is similar across regions of the world, in contrast to the overall morbidity of prostate cancer.[3] It is generally believed that latent prostate cancer does not commonly grow into clinically apparent cancer, however, some of the latent prostate cancers may slowly grow into a clinical cancer.[4-6]

Since prostate cancer and benign prostatic hypertrophy (BPH) occur due to similar etiologies and at similar ages, both prostate cancer and BPH may be identified simultaneously in the same man. It has been reported in Japan and other countries that prostate cancer was found in 4–7% of men presenting to the outpatient sections of hospitals with dysuria.[7,8] Therefore, it is necessary to investigate patients presenting

with any urinating trouble to an outpatient section/clinic for the presence of prostate cancer by prostate specific antigen (PSA) testing and digital rectal examination (DRE).

Although the determinate risk factor of prostate cancer remains unknown, some plausible risk factors have been identified. Presently the strongest risk factor of prostate cancer is heredity. The risk of prostate cancer is increased if a family has multiple prostate cancer patients or a prostate cancer patient with onset at a younger age.[9] Since prostate cancer represents an androgen-dependent cancer, the presence of androgens is essential for the onset of prostate cancer. An extrinsic factor that is suggested to contribute to the risk of prostate cancer is the Western style of diet in which animal fat is frequently ingested, although this has not been definitively validated.[10] The incidence of prostate cancer is negatively correlated with the regular ingestion of beans and grains and positively correlated with the active ingestion of sugar, milk, and fat.[11] Selected chemicals, including selenium; β carotin; vitamins A, E, D, and C; isoflavone; and lycopene, are being researched for possible preventive effects against prostate cancer.[12–15]

3. Screening

Since the PSA test provides the convenient and accurate detection of prostate cancer, it is used as a useful primary screening for prostate cancer. The guidelines of the American Cancer Society and the American Urological Association advocate that men aged over 50 years (45 or 40 years for black men and individuals with a familial history of prostate cancer) should be provided with an explanation about the merits and demerits of screening for prostate cancer. These guidelines recommend that a PSA test and DRE should be conducted for those who wish to check for prostate cancer.[16,17] On the other hand, the American College of Preventive Medicine and the American College of Physicians have indicated that there is so far no evidence for recommending or not recommending the routine practice of screening for prostate cancer and have stated that a man who is going to have a medical checkup should decide whether or not to undergo screening for prostate cancer at his own discretion after receiving information about the screening and the subsequent treatment for prostate cancer.[18,19]

The contribution of the introduction of screening for prostate cancer for decreasing the mortality of men has been validated by the data obtained in an epidemiological study in Olmstead County, Minnesota, USA;[20] epidemiological data collected in Quebec, Canada;[21] and an intervention study in Tyrol, Austria.[22] A prostate, lung, colorectal and ovarian cancer screening study (PLCO)[23] and European randomized study of screening for prostate cancer (ERSPC)[24] are large-scale randomized controlled studies currently ongoing in the USA and Europe, respectively.

There is an increase in the adoption of prostate cancer screening for local government-sponsored mass screening around Japan. PSA-based prostate cancer screening has also been included in complete physical examination, with an increasing number of individuals undergoing it. The prostate cancer detection rate by screening using PSA alone has been reported to be 0.09% in men of 50–54 years old, 0.22% in men of 55–59 years old, 0.42% in men of 60–64 years old, 0.83% in men of 65–69 years old, 1.25% in men of 70–74 years old and 1.75% in men of 75–79 years old.[25] An increased detection rate of early cancer has also been shown as a result of the introduction of prostate cancer screening.[26] It is also possible to set up a schedule for undergoing prostate cancer screening based on the baseline PSA test value. Investigations have thus been performed for the contribution of prostate cancer screening to the improvement of the cost-benefit ratio.[27,28]

Since the PSA test involves false negative as well as false positive results at the present and since cancer cells can elude a needle biopsy, screening for prostate cancer may cause drawbacks for recipients due to the issue of the accuracy of the test method and the complications of treatment. Nevertheless, in the USA, about three quarters of the male population aged over 50 years have been checking the PSA value despite the fact that varied levels of recommendation for prostate cancer screening have been issued by different medical societies/associations. It has been forecast that the morbidity of prostate cancer and the incidence of death from prostate cancer will increase in the future in Japan as well. Taking these facts into consideration, it is worthwhile making the merits and demerits of screening for prostate cancer widely known to the general public in Japan by distributing informative leaflets, etc. and to organize a structure that can provide an optimal screening program for prostate cancer to individuals wishing to check the presence/absence of prostate cancer.

4. Japanese prostate cancer registration program

The Japanese Urological Association has made the Japanese Prostate Cancer Registration Program into a CD-ROM and attached it to the Third Edition (issued in April 2001) of the General Rules for Clinical and Pathological Studies on Prostate Cancer to provide a system for extensive survey into the epidemiology, diagnosis, treatment, and prognosis of Japanese patients with prostate cancer. A total of 4529 prostate cancer patients diagnosed in 2000 at 173 institutions were registered and the clinical features of these patients were reported in 2005.[29] It is expected that accurate trends of prostate cancer in Japanese men will become elucidated along with an increase in the number of institutions participating in this registration program and the accumulation of follow-up data for registered patients.

B. Diagnosis

1. Digital rectal exam, PSA, and transrectal ultrasonography

An abnormality is detected by DRE in 15–40% of all patients diagnosed with prostate cancer, although this is in part dependent on the extent of the experience of the examining physician. When DRE has been performed in asymptomatic men who are not suspected for prostate cancer, the tumor detection rate was reported to be as low as 0.1–4%[30,31] (V).

PSA is kallikrein-like serine protease released from the prostate gland epithelium. It is clinically prostate gland-specific but not specific to prostate cancer. Therefore, PSA levels may also be increased due to BPH, prostatitis or other benign prostatic diseases. The PSA test is, however, more sensitive than DRE and transrectal ultrasonography as an independent predictor of prostate cancer[32] (III).

A variety of PSA assay kits are commercially available now, however none of the products have been recognized as an international standard. Prostate cancer is detected by biopsy in 25–30% of men with PSA levels of 4–10 ng/mL and 50–80% of men with PSA levels ≥ 10 ng/mL[33] (III). It has generally been believed that prostate biopsy should be indicated for men who have PSA ≥ 10 ng/mL (but it is actually indicated at PSA ≥ 4 ng/mL) with no palpable tumor.

It should be noted that clinically insignificant cancer may be detected by biopsy by adopting a low level PSA threshold. To date, long-term clinical data remain unavailable to allow the recommendation of the optimal PSA value for the detection of prostate cancer which is impalpable but of clinical significance.

The following subclasses of PSA have been proposed to raise the specificity of PSA testing and the detection rate of early prostate cancer. They are PSA density, PSA density in the transitional zone, age-specific reference ranges of PSA thresholds, PSA molecular forms, PSA velocity, and PSA doubling time. These PSA subclasses may be useful to some extent for the differentiation of prostate cancer from BPH, particularly in men with PSA of 4–10 ng/mL. However, the introduction of these PSA subclasses to general healthcare practice remains controversial[34,35] (III).

Such an expanded utilization of PSA in an attempt to detect prostate cancer early has led to the creation of a new category of disease stage: T1c. T1c denotes cancer detected by biopsy indicated due to a high PSA value in the absence of abnormality on DRE and imaging diagnosis. Clinical and histological investigations have revealed that 11–26% of T1c prostate cancers were clinically insignificant whereas 18–49% represented localized invasive carcinoma[36] (III).

Transrectal ultrasonography is very beneficial for (1) the identification of the involved region and (2) the improvement of the precision of prostate biopsy. However, it is practically impossible to detect prostate cancer only by transrectal ultrasonography while no abnormality is found using DRE and a PSA test. A color Doppler probe for transrectal ultrasonography remains a prototype and has not yet been included in routine examinations for the detection and staging of prostate cancer.

Screening for prostate cancer that combines DRE, PSA, and transrectal ultrasonography attains a positive predictive value (PPV) of 20–80%. Prostate cancer is confirmed by biopsy in 6–25% of men who are shown to be positive in only one of these three tests, 18–60% of men who are positive in two of the above three tests, and 56–72% of men who are shown to be positive in all of the three tests[37] (II),[38] (III).

A man of linear kin (father or brother) to one or more prostate cancer patients would have more chances of detecting prostate cancer in the early stage by checking his PSA value[39] (II).

2. Prostate biopsy

Transrectal ultrasound-guided insertion of an 18-G needle is the standard prostate biopsy procedure for the pathological diagnosis of prostate cancer[40] (III). Either transrectal or transperineal access is used. These routes of prostate biopsy differ with respect to the anesthetic method, the site of specimen collection and complications, while it is difficult to judge which is more advantageous[41] (II),[42,43] (III). When a palpable nodule exists, target biopsy is indicated. However, when the patient is a candidate for radical prostatectomy and diagnostic accuracy should be increased, systematic biopsy is recommended. In recent years, sextant biopsy specimens tend to be collected from sites extending up to the lateral rim of the prostate, aiming to improve the cancer detection rate of prostate biopsy[44,45] (III). Prostate biopsy specimens collected in such a manner contain the posterior lateral side of the periphery, in which early prostate cancer is most frequently located.

When a repeat biopsy is performed for a man who has been shown to be negative in the first biopsy but continues to have symptoms suggestive of cancer, cancer is reportedly detected by repeat biopsy at a rate of about 20%[46,47] (III). However, no definitive criteria for repeat biopsy have been established. If high-grade prostatic intraepithelial neoplasia (PIN) or atypical small acinar proliferation (ASAP) is found, cancer is believed to coexist at a high incidence of 50–100%.[48,49] Therefore, repeat biopsy is recommended in such a case.

3. Staging

For the staging of prostate cancer at initial diagnosis, not only DRE, a PSA test and bone scintigraphy are performed but also computed tomography (CT)/ magnetic resonance imaging (MRI). A chest X-ray is also performed in certain cases.

1) T staging

Initially, it should be distinguished whether a cancer is confined within the prostate capsule (T1, T2) or has spread beyond the prostate capsule (T3, T4). This is very important for the decision regarding a subsequent treatment strategy. As DRE is apt to underestimate local infiltration, the rate of coincidence between staging on DRE and histopathological staging has been reported to be less than 50%[50] (III). However, further detailed evaluation of the primary lesion is recommended only when it is directly involved in making a treatment strategy or when radical prostatectomy is projected.

A PSA value increases with the progression of the disease stage. However, there are limitations in accurately predicting the final histopathological stage on the basis of an individual PSA value. A combination of PSA value, the Gleason score of the biopsy specimen and clinical staging is useful for the estimation of the final histopathological stage[51] (III). Transrectal ultrasonography is not recommended as a routine testing for staging diagnosis since it is inadequate for accuracy in elucidating tumor extension[52] (III). Seminal vesicle biopsy should be considered for patients whose treatment strategy may be modified according to the involvement of the seminal vesicle. In addition, more detailed analysis of the results of multifocal biopsy (with respect to the number of positive specimens, tumor grade and extension, and capsule penetration) may be useful.

CT may not be adequately accurate for the evaluation of local infiltration of neoplasm[53] (IV). MRI has been reported to be useful for the identification of the stage of locally advanced disease (e.g. extracapsular involvement and seminal vesicle involvement).[54,55] However, MRI is still controversial for the introduction to routine practice for preoperative staging of prostate cancer.

2) N staging

Evaluation of the lymph nodes is only indicated when it is directly involved in making a treatment strategy. This is usually applicable to a patient who chooses radical prostatectomy. A patient who has a high PSA value, T2b or T3 lesion, poorly differentiated carcinoma or perineural involvement is at a high risk of lymph node involvement[56] (IV). It is difficult to predict the presence/absence of lymph node involvement in individual patients based only on a PSA assay. The accuracy of predicting lymph node involvement can be increased by combining PSA assay, DRE and tumor grade.[56]

This is also applicable, in turn, to patients at a low risk ($\leq$10%) of lymph node involvement. For a patient who has a PSA value $\leq$ 20 ng/mL + T2a lesion + Gleason score $\leq$ 6, it is warranted to omit the evaluation of lymph node involvement before carrying out radical prostatectomy[56] (IV).

For the evaluation of lymph node involvement, the optimal approach is lymph node dissection by open surgery or laparoscopic surgery. Since both CT and MRI have low sensitivity with an accuracy of 0–70% for the evaluation of lymph node involvement, the usage of these diagnostic modalities is limited.[54]

3) M staging

Metastasis to the vertebral body is detected in 85% of patients dying of prostate cancer.[57] The presence and progression of bone metastasis exactly reflects the prognosis of individual patients. Bone scintigraphy is the most sensitive diagnostic modality for the detection of bone metastasis[58] (III). Semi-quantitative evaluation of bone lesion on bone scintigram has been shown to be correlated with the prognosis of prostate cancer patients[59] (III). Prostate cancer can metastasize to various organs other than the bone. For instance, prostate cancer metastasizes to the distant lymph nodes, liver, lungs, brain, and skin. When metastasis to the soft tissues is suspected, the patient has indications for all of the diagnostic modalities including routine check-ups, chest X-rays, ultrasonography, CT and MRI.

A pre-treatment PSA value ≥ 100 ng/mL means, by itself, the presence of metastatic lesion with a probability of approximately 100%[60] (IV). Rarely, however, bone metastasis may be found even in a patient who has a low PSA value. A PSA value ≤ 20 ng/mL reflects a status of prostate cancer without bone metastasis with a probability of approximately 99%[61] (III). It has been reported that bone scintigraphy is not required for disease staging in a patient who is asymptomatic with a PSA value ≤ 10 ng/mL and a well- or moderately differentiated carcinoma[62] (III).

C. Treatment overview

1. History of treatment modality

Four therapies are currently widely used for the treatment of prostate cancer: (1) surgery (2) radiation therapy (3) pharmacotherapy (endocrine therapy) and (4) expectant management. The details of each therapy are described in the respective sections. The present section introduces the overall profile of the treatment for prostate cancer. The first effective treatment for prostate cancer was achieved in 1941 by Huggins and his colleagues, who performed castration in a man with progressive prostate cancer and obtained some improvement of the patient's symptoms and examination findings. Since then, endocrine therapy has been performed as a gold standard therapy for prostate cancer. However, it was found that the endocrine-dependent nature of prostate cancer becomes depleted and the disease relapses during long-term endocrine therapy. Formerly, prostate cancer has commonly been found to be progressive at the time when it is diagnosed. Since around 1990, when PSA was introduced as a diagnostic indicator of prostate cancer, localized prostate cancer has come to be commonly detected. Total prostatectomy has been introduced as a radical treatment of localized prostate cancer and has widely prevailed today as a standard therapy for localized prostate cancer. Furthermore, a remarkable advancement has been made in the technique of radiation therapy, and both radiation therapy and total prostatectomy are offered as a standard therapy for localized prostate cancer. Expectant management of prostate cancer is a method for watching the prostate cancer patient without treatment even after it has been diagnosed until an appropriate time when intervention is considered to be necessary. Expectant management is characteristic to prostate cancer and can be a beneficial treatment option because surgery, radiation therapy and endocrine therapy for prostate cancer significantly impact on sexual function; because PSA is available as a sensitive tumor marker for assessing the status of disease; and because some prostate cancers are biologically minimally malignant.

2. Issue of literature analysis

The results of Japanese clinical studies that have involved Japanese prostate cancer patients have been incorporated, as much as possible, into the source data used when devising the present guidelines. Nevertheless, the majority of clinical studies concerning prostate cancer have been conducted abroad, and the treatment recommendations and grades of recommendations in the present guidelines were eventually determined based on overseas clinical data. So far, it has not been confirmed to be reasonable to apply overseas clinical study data directly to Japanese individuals. In fact, there are data showing that the incidence of clinically significant prostate cancer and the progression speed from latent cancer to clinically apparent cancer differ between foreign patients and Japanese patients. Therefore, the working group emphasizes that recommendations presented herein need to be carefully interpreted for application to clinical practices.

3. Surgery

(1) Evidences for surgery

Radical prostatectomy is the standard technique of surgical treatment, in which the prostate gland and seminal vesicle is removed and the bladder neck is anastomosed to the urethra. In general, the obturator lymph nodes are dissected simultaneously. A retropubic approach to the prostate is most common while a perineal approach or laparoscopic resection is also used according to institutional strategy.

Since it is relatively difficult to perform a randomized controlled trial (RCT) for the evaluation of surgical treatment, the evidence level for the recommendation of surgical treatment is lower in general. In this context, there is a comment that numerous findings are available from comparative studies other than RCT as well as observatory epidemiological surveys but treatment recommendations should be supported by adequate evidence.[63] It is also necessary to consider whether or not the malignant potential of prostate cancer in Japanese patients is equal to that in American and European patients.

(2) Endpoint of surgery

Since the prognosis of localized prostate cancer is generally favorable after prostatectomy, survival, which is generally used as an endpoint of cancer treatment, hardly serves as an endpoint of surgical treatment for prostate cancer. Therefore, a PSA failure is used as a surrogate endpoint. However it is disputable whether a PSA failure can really be an adequate surrogate endpoint or not. It has been suggested that PSA failure can be a valid surrogate endpoint in high risk patients[64] (IV),[65] (III),[66] (IV) while PSA failure is not correlated with survival in low to intermediate risk patients[67-69] (III),[70] (IV). Thus, PSA doubling time (PSADT), which is considered to depend on the growth speed of remnant cancer cells after prostatectomy, may be a more appropriate endpoint[66] (IV),[67] (III).

(3) Curability of radical prostatectomy

Radical prostatectomy for localized prostate cancer is very likely to provide a curative treatment[71,72] (II). Taking into account the safety of the current surgical procedure of prostatectomy and the availability of salvage radiation therapy and endocrine therapy for postoperative relapse, radical prostatectomy is considered to result in most long-term survival. However, it has been reported that endocrine therapy delayed by expectant management is comparable to radical prostatectomy in terms of the 10-year disease-specific survival rate in patients with a

Gleason score of 2–4[71] (II),[73] (III). Taking the improved outcomes of radiation therapy in recent years also into consideration, radical prostatectomy cannot be concluded to be definitively superior to expectant management-delayed endocrine therapy and radiation therapy[74] (II).

(4) Curability of radical prostatectomy

The ideal indication criteria for radical prostatectomy may be defined as a life expectancy ≥10 years + PSA < 10 ng/mL + Gleason score ≤ 7 + T1c to T2b lesion[75–79] (III). In this patient population, the five-year PSA relapse-free postoperative survival rate is 70–80%, and the 10-year PSA relapse-free survival rate is 50–70%[80–84] (III). Concerned postoperative complications include urinary incontinence and the impairment of erectile function.

Meanwhile, no reason is established for excluding localized prostate cancer in an elderly patient from the option of radical prostatectomy where there is a Gleason score ≥ 8, PSA ≥ 20 ng/mL, or T3 disease[85–87] (III). As a matter of course, radical prostatectomy is not always indicated in such patients. It is important to consider life expectancy and quality of life (QOL) when making a decision regarding radical prostatectomy[88] (IV),[89] (III). Since the accumulated experience of the surgeon in radical prostatectomy is related to outcomes of surgery and the extent of postoperative complications[90] (II),[91] (III), radical prostatectomy for localized prostate cancer with a Gleason score ≥ 8, PSA ≥ 20 ng/mL, or T3 disease in an elderly patient should be performed by an experienced urologist who is able to cope with extensive local resection and surgical complications[92] (II).

(5) Neoadjuvant endocrine therapy

RCTs showed that three-month neoadjuvant endocrine therapy is not effective in the improvement of results of radical prostatectomy, so three-month neoadjuvant endocrine therapy is not recommended[93–95] (II). However, further studies are required with regard to the benefits of neoadjuvant endocrine therapy, such as the longer survival period and its relevance as a treatment for localized advanced prostate cancer. Only limited benefits can be obtained with monotherapy.

(6) Surgical procedures

Radical prostatectomy is performed usually via the retropubic approach, the perineal approach or the laparoscopic approach. Each of these procedures seems to have an individual disadvantage[96] (III), and there is no robust evidence to determine which procedure is best.

Reportedly, the positive surgical margin is commonly found in the apex of the prostate when prostatectomy is performed via the retropubic approach, in the bladder neck according to the perineal approach and on the lateral posterior side of the prostate according to the laparoscopic procedure[97] (III). Issues characteristic to the retropubic prostatectomy procedure include massive bleeding and the marked incidence of postoperative inguinal hernia[98,99] (III). The perineal procedure is characterized by rectal complications[98–101] (III). Laparoscopic radical prostatectomy has been reported to be more frequently associated with postoperative complications when it is performed by an inexperienced surgeon[102] (III),[103] (II),[104] (III),[105] (III).

Although urinary incontinence is a major morbidity of radical prostatectomy, there is no evidence to recommend the sparing of the pubic prostate ligament or the bladder neck. It has been indicated that there is a risk of the presence of cancer cells in the margin of the resected specimen in sparing the bladder neck if the prostate capsule has been involved[106] (III). A large-scale follow-up survey revealed that urinary continence is unsatisfactory, more than expected by the treating physician and surgeon[107] (III).

No criteria have been established for the safe indication of nerve sparing radical prostatectomy[108] (IV). Moreover, it has been revealed that sexual function is impaired more severely than was expected by healthcare providers[109] (I).

When the nomogram of Japanese patients with prostate cancer has been compliled, it may become possible to identify a patient who allows one to exclude lymph node dissection[110] (III). Regarding 'whether expanded lymph node dissection can provide survival benefit or not', the conclusion may be dependent on the disease status of the patient indicated for radical prostatectomy. An RCT that involved a substantial number of low-grade, low-stage patients concluded that expanded lymph node dissection had no meaning for survival benefit[110] (II). In contrast, another RCT that predominantly involved high-risk patients showed that expanded lymph node dissection had meaning and concluded that it is appropriate to remove the internal and external lymph nodes and obturator lymph nodes[111] (III). Therefore, no recommendation can be made up with regard to lymph node dissection.

(7) Postoperative follow-up and diagnosis of recurrence

It is a dominant opinion that the cut-off for PSA failure should be 0.2 ng/mL in patients receiving no adjuvant therapy after radical prostatectomy, and this seems to be realistic[67,69,112] (III). In general, PSA failure has been recognized as the first event of recurrence. It has been reported that recurrence or metastasis can take place in the presence of an undetectable level of PSA, but this is very rare and may be limited to the case of undifferentiated carcinoma[68,113] (III). Therefore, it is unnecessary to consider extra-examination such as DRE so long as a patient is free from PSA failure[68,113–115] (III).

(8) Post-recurrence treatment

In an RCT, prostate cancer patients who were found to have involved lymph nodes during radical prostatectomy were divided into two groups to begin endocrine therapy in the stage of clinical failure (not PSA failure) and to receive adjuvant therapy immediately. This study showed that patients who received adjuvant therapy immediately had a better prognosis[116] (II). In patients who have pT3 (to 4) N0 M0 disease, adjuvant radiation therapy may decrease the risk of PSA failure[117–119] (III). Nevertheless, even in a patient with pT3 N0 M0 disease, adjuvant radiation therapy is likely to be ineffective if he has a Gleason score of 7–10, pT3b disease or a preoperative high PSA value (≥25 ng/mL)[120] (III). Furthermore, it was reported that patients who have a positive surgical margin plus a Gleason score of ≥8 plus preoperative PSA value > 10.9 ng/mL are still at a high risk of recurrence even when undergoing adjuvant radiation therapy[121] (III).

It is controversial whether to introduce radiation therapy as an adjuvant therapy for postprostatectomy patients or as a rescue treatment after PSA failure in such patients. There is a report advocating that adjuvant radiation therapy is more advantageous[122] (III), and another report insists that the outcome is equivalent between adjuvant radiation therapy and rescue radiation therapy started after the occurrence of PSA failure[123] (II). So, no consensus has been reached yet in this aspect.

4. Radiation therapy

(1) History of radiation therapy

Radiation therapy (RT) can be largely classified into external beam and interstitial irradiation according to the mode of treatment. Assisted by the great advancement of computer technology, an innovative change has been brought about to RT for prostate cancer. Since RT therapy is a local therapy, like radical prostatectomy, it is best indicated for localized cancer, generating comparable results with those of radical prostatectomy[124] (III). However, based on the long-term results of large-scale randomized studies conducted from the middle of the 1980s through the 1990s in the USA and Europe, it has been recognized that the overall survival rate can be increased even in patients with locally advanced prostate cancer by combining RT with endocrine therapy (neoadjuvant or adjuvant) and in more recent years, a marked modification has been thus made to the treatment strategy for prostate cancer[125-131] (II),[132] (III),[133-135] (II). Because the indications and treatment options of RT have been expanded, it has been advocated to stratify individual patients by risk stratification on PSA, biopsy Gleason score, and clinical stage, in order to choose the optimal treatment strategy[136] (III),[137] (II),[138] (III). Usually, the risk categories of prostate cancer patients are broadly stratified into low, intermediate and high risk, although there is no consensus about the definition of these risk classes. So, the details for each risk stratification differ from study to study.

Moreover, in recent years, not only the results of the specific treatment strategy but also the cost, possible complications and side-effects, toxicity, and QOL tend to be taken into account when a first-line therapy is chosen. It is important to consider RT strategies from such viewpoints. Otherwise, RT is often indicated as palliation therapy and salvage treatment for recurrence after other first-line therapies.

(2) External beam radiation

Radiation strategies available in Japan include conventional photon beam radiation with linear accelerator, three-dimensional conformation radiation therapy (3D-CRT), and intensity modulated radiation therapy (IMRT). Particle beam RT is also performed, although this is available only in limited institutions and has not been covered by the : Please provide an expansion for the abbreviation National Health Insurance(NHI) reimbursement scheme. To obtain local control of cancer using external photon beam radiation alone, a dose ≧ 70 Gy is necessary according to the fractionated RT[139] (II). Various treatment techniques have been developed to administer a sufficient dose effectively while suppressing the incidence of adverse events.

It is still controversial whether radiation should target the prostate alone or whether the whole pelvic radiation should be combined. However, a study by the Radiation Therapy Oncology Group 9413 showed a significant improvement of relapse-free survival rate in a cohort treated by whole pelvic radiation + neoadjuvant/concomitant endocrine therapy.[134] (II).

Regarding the duration of adjuvant endocrine therapy, a long-term therapy (>24 months) is generally believed to be necessary for high-risk patients. For intermediate-risk patients, a benefit was obtained even with a shorter-term adjuvant therapy for six months, while it was suggested that low-risk patients do not need adjuvant endocrine therapy[125-131] (II),[132] (III),[133-137] (II),[136] (II). However, further studies are necessary to elucidate what regimen of endocrine therapy is optimal and how long it should be administered.

(3) Interstitial radiation

^{125}I permanent brachytherapy and ^{192}Ir high-dose-rate interstitial RT are among the representative interstitial RT currently available in Japan. The ^{125}I permanent brachytherapy, which has been widely used in the USA, is performed by implanting radioactive metal chips in the prostate under ultrasound guidance. In Japan, this radiation method was approved in March 2003. ^{125}I permanent brachytherapy is commonly done as monotherapy in low-risk patients and in combination with external radiation in some intermediate- and most high-risk patients[140] (III),[141] (II). No prospective randomized controlled study has been conducted to date for the evaluation of the efficacy of brachytherapy + endocrine therapy. This is because seed implantation alone is best indicated for low-risk patients, who do not necessarily require endocrine therapy to maximize disease control. Usually, ^{192}Ir high-dose-rate interstitial RT is combined with external radiation and is indicated to treat localized, regional or invasive prostate cancer. Complications associated with either interstitial or external RT include rectal dysfunction, dysuria, and erectile dysfunction.

(4) Relapse after radiation therapy

Much debate has been made with regard to the definition and implications of biochemical and clinical recurrence after RT[142] (IV),[143] (III),[144] (IV), and[145] (II). Arguments generally have been focused on the implications of post-therapy biopsy for the evaluation of clinical relapse timing of serum prostate-specific antigen (PSA) tests, and criteria for significant changes in PSA for the evaluation of biochemical relapse.

5. Pharmacotherapy

(1) Endocrine therapy for prostate cancer

None of the currently available chemotherapies exceed endocrine therapy for the treatment of prostate cancer. Different endocrine medications are remarkably proximate in their efficacy for the control of prostate cancer, whereas their efficacy lasts no longer than two to three years in the case of progressive disease. Furthermore, endocrine therapy causes sex-related adverse reactions such as erectile dysfunction (ED) and impairment of the libido[146,147] (II). Because of these issues, endocrine therapy has limitations in its indications.

The first attempt of effective endocrine therapy was made by performing surgical castration. Female hormone preparations were used subsequently, but they are now seldom used due to adverse cardiovascular reactions. The most commonly used endocrine medications are luteinizing hormone-releasing hormone (LH-RH) agonists and anti-androgens, which are used either as monotherapy or combined therapy. As LH-RH agonists, one-month and three-month formulations of goserelin or leuprorelin are available. Steroidal and non-steroidal anti-androgens have been approved in Japan. LH-RH agonist therapy causes a transient rise in testosterone level in the early treatment stage, ensuing flare-up symptoms such as urinary tract obstruction, bone pain arising from metastatic lesions, and bone marrow compression. When such adverse reactions are concerned, combined use with an anti-androgen should be considered. The efficacy of an LH-RH agonist is considered to be equivalent to that of surgical castration, while the efficacy of anti-androgen alone has been reported to be weaker than an LH-RH agonist although no significant difference has been shown. Nevertheless, because non-steroidal anti-androgens are associated with less sex-related adverse reactions, anti-androgen monotherapy has been indicated to be beneficial for selected patients. The benefit of

bicalutamide adjuvant therapy was evaluated in patients with localized regional or invasive prostate cancer who had undergone radical prostatectomy, radiation therapy and watchful observation. The study showed a significant prolongation of PSA doubling time and a reduction in objective progression risk[148 150] (II).

A large-scale study is ongoing now for the assessment of the survival benefit of bicalutamide adjuvant therapy.

Another issue being investigated is whether chemo-endocrine therapy is more beneficial for Stage IV patients than endocrine monotherapy.

(2) Validity of maximum androgen blockade (MAB)

In Stage III-IV prostate cancer patients, the survival benefit of endocrine therapy has been validated[151] (II). In general, the standard therapy for metastasized advanced prostate cancer is androgen blockade by utilizing surgical (orchiectomy) or pharmaceutical (LH-RH agonist) castration. Testis-derived androgen is controllable by surgical or pharmaceutical castration. Reportedly, however, 40% of androgen existing in the prostatic cells is derived from the adrenal. Thus, maximum androgen blockade (MAB) therapy, which inhibits both testis- and adrenal-derived androgen by combining castration with non-steroidal anti-androgen, was evaluated and shown to be useful[152] (III). Since then, MAB has come to be widely used as a treatment modality for advanced prostate cancer. Nevertheless, an issue that has been discussed is whether MAB improves long-term survival when compared with castration alone. A meta-analysis performed in the early days that included data with steroidal anti-androgens showed no significant difference for survival time between MAB therapy and castration alone[153] (I). Another meta-analysis performed by excluding data with steroidal anti-androgens (involving 2922 patients from 13 studies) revealed that MAB therapy is significantly superior in terms of both relapse-free survival time and overall survival time. Likewise, a recent meta-analysis also showed a significant increase in overall survival rate in patients receiving MAB using non-steroidal anti-androgens[154] (I).

Meanwhile, in a large-scale RCT conducted by the Southwest Oncology Group (SWOG)[155] (II), surgical castration + flutamide treatment was compared with surgical castration + placebo treatment, and no significant difference was found in terms of the overall survival rate. A recent meta-analysis that involved all the above RCTs indicated that MAB therapy is similar to castration alone in terms of a two-year survival rate whereas MAB therapy is significantly superior to castration alone in terms of a five-year survival rate[156 158] (I). However, since the difference in the survival rate was small, it was indicated that the true clinical benefit of MAB should be judged by taking into account efficacy, adverse reactions, QOL, and the medical financial aspect. Recently, a double blind study was conducted for comparison between MAB therapy, which used bicalutamide as an anti-androgen, and LH-RH agonist monotherapy; it was found that the MAB therapy obviously prolonged the time to progression.

(3) Pharmacotherapy for recurrent cancer

When recurrent cancer is judged to be present, exacerbation may be transiently inhibited by withdrawing only the anti-androgen therapy (anti-androgen withdrawal syndrome). A decrease in PSA can be obtained in 14–60% of patients and clinical response in 0–25% of patients by withdrawing only the anti-androgen therapy or by combining hydrocortisone. However, it has been reported that the response of PSA is usually maintained no longer than 2–4 months.

Anticancer chemotherapy using a single drug or multiple drugs has been attempted for the control of relapsed cancer during endocrine therapy. Drugs used for single-drug anticancer chemotherapy include estramustine phosphate, CPA, fluorouracil (FU), and etoposide (ETP). However, none of the randomized controlled trials conducted so far showed an obviously extended survival time as a result of the introduction of chemotherapy. It was recently reported that docetaxel (TXT) + steroid[159] (II) or TXT + estramustine phosphate[160] (II) significantly increased the survival rate when compared with mitoxantrone + steroid. Presently, estramustine phosphate and FU have been covered by the NHI reimbursement scheme for the treatment of prostate cancer, while other chemotherapy drugs have not been approved for the treatment of prostate cancer.

6. Expectant management: watchful waiting

(1) Definition

Expectant management means, in a broad sense, to put off intervention until it becomes necessary in a patient diagnosed as having prostate cancer. Expectant management is pursued on the assumption either to introduce endocrine therapy as the second-line therapy for clinical progression (watchful waiting with deferred endocrine therapy) or to carry out radical intervention consisting of radiation therapy and/or radical prostatectomy as the second-line therapy in an appropriate timing (active surveillance; expectant management in a narrow sense). The present guidelines discriminate active surveillance from watchful waiting with deferred endocrine therapy, and this section individually provides guidance for the two modes of expectant management.

(2) Watchful waiting with deferred endocrine therapy for advanced prostate cancer

For patients with advanced prostate cancer, the advantage/disadvantage of immediate endocrine therapy versus watchful waiting with deferred endocrine therapy remains indefinitive. About half of patients with metastasizing prostate cancers experience relapse within 18–24 months and die within 30–36 months. Taking this into consideration, there will be a slight difference depending on whether watchful waiting with deferred endocrine therapy or immediate endocrine therapy is chosen. Watchful waiting with deferred endocrine therapy for metastasizing prostate cancer is not recommended by the Physicians Data Query (PDQ) for Prostate Cancer presented by the National Cancer Institute (NCI) nor by the Guidelines for Prostate Cancer of the European Association of Urology (EAU).

(3) Watchful waiting with deferred endocrine therapy for localized prostate cancer

The comparison of surgery versus watchful waiting with deferred endocrine therapy was performed for patients with localized prostate cancer. A large-scale randomized controlled trial (RCT) was conducted mainly in Northern Europe to compare radical prostatectomy versus watchful waiting with deferred endocrine therapy in patients with localized prostate cancer, and the results of this study have been published[161] (II). Radical prostatectomy increased the prostate cancer-specific survival rate but not the overall survival rate in patients with moderately- to highly-differentiated localized prostate cancer. However, the results of analysis including data from the extended post-hoc follow-up period

revealed that both the overall survival rate and prostate cancer-specific survival rate were superior in the cohort treated with radical prostatectomy[162] (II).

Combining non-randomized clinical trials in patients with localized prostate cancer that were reported between 1985 and 1992, a meta-analysis was performed to analyze the benefit of watchful waiting with deferred endocrine therapy. A total of 828 patients were involved, and the 10-year prostate cancer-specific survival rate for patients with Grade 1 or Grade 2 carcinoma was shown to be 87% while the corresponding survival rate for patients with Grade 3 lesion (Gleason score of 8–10) was as low as 34%[163] (II). Thus, it was indicated that tumor grade is the major prognostic determinant of watchful waiting with deferred endocrine therapy in patients with localized prostate cancer.

(4) Active surveillance for localized prostate cancer

Since PSA-based monitoring has become prevalent today, a comparison was made between radical prostatectomy immediately performed in patients with early prostate cancer and radical prostatectomy performed after PSA-based watch but before progression of the lesion into invasive prostate cancer. With regard to the type of patients that should be treated for PSA watch management, the criteria may be made up of a Gleason score of ≥6, PSA ≤ 20 ng/mL, and a clinical stage of T1 to T2, although no consensus has yet been obtained. Life expectancy and the risk of needle biopsy-mediated cancer dissemination should also be taken into account. During active surveillance, a DRE and PSA check should be implemented every three to six months, and repeat biopsy should also be done as necessary. As for the timing to proceed to a second-line therapy, PSA doubling time was generally considered in reported studies, and the second-line therapy was commonly introduced in patients who had PSA doubling within two years[164,165] (III).

Due to the prevalence of the PSA test, low-risk prostate cancer tends to be more frequently detected. Nevertheless, the US data indicate that patients who choose active surveillance have been decreasing in number. This trend for a decreased percentage of patients undergoing active surveillance reflects an increase in the percentage of patients undergoing brachytherapy and endocrine therapy[166] (III). Both the circumstances of the healthcare providers and the patient's preference in choosing a treatment option may be underlying reasons for the change in the choice of treatment option, while further detailed analysis involving a QOL survey is awaited. While information is still insufficient to compare QOL across treatment options for prostate cancer, a cross-sectional data analysis was conducted in the USA, involving approximately 800 patients. This analysis revealed that patients on active surveillance experienced a significant deterioration of QOL in terms of the physical functioning and the general health perception out of the eight subscales of the RAND SF-36 when compared with patients who were immediately treated with radical prostatectomy. Nevertheless, patients on external radiation therapy or endocrine therapy had significant deterioration of QOL in terms of virtually all of the 8 subcategories of the SF-36 as compared with patients with radical prostatectomy. Based on these results, it seems unlikely that the deterioration of QOL during active surveillance is an exact reason for patients not to choose active surveillance[167] (III). A likely reason seems to be that patients would generally feel uneasy about being left without treatment despite the disclosed diagnosis of cancer. Whether a patient chooses active surveillance or not would be greatly affected by the physician's explanation[168] (IV). Therefore, it is thought to be an urgent need to compile scientific information that is useful for the counseling of prostate cancer patients, especially data for Japanese prostate cancer patients. Currently, a feasibility study is ongoing in Japan to evaluate active surveillance treatment for patients suggested to have a well differentiated carcinoma that is small in size according to the predefined criteria[169] (III)

7. Indications for therapeutic modalities

(1) T1a, N0, M0 prostate cancer

(1) T1a, N0, M0 prostate cancer with a Gleason score ≤ 6

T1a prostate cancer with a Gleason score ≤ 6 is generally highly differentiated and localized. Most T1a prostate cancer patients do not require any specific treatment other than active surveillance. For younger (50–60 years old) patients, however, use of definitive treatments such as radical prostatectomy or radiation therapy should be considered as they have longer life expectancy.

(2) T1a, N0, M0 prostate cancer with a Gleason score ≥ 7

Active surveillance is a recommended treatment option for T1a prostate cancer with a Gleason score ≥ 7. Definitive treatment may be considered for younger patients whose life expectancy is at least 15 years.

(2) T1b-c/T2, N0, M0 prostate cancer

(1) T1b-c/T2, N0, M0 prostate cancer with a Gleason score ≤ 6 with serum PSA ≤ 20 ng/mL

Therapy options recommended for T1b-c/T2 prostate cancer with a Gleason score ≤ 6 with serum PSA ≤ 20 ng/mL include radical treatments (total prostatectomy and radiation therapy) and active surveillance. In any case, definitive treatment is selected for patients whose life expectancy is at least 10–15 years at the time of treatment, while endocrine therapy or irradiation may be indicated for patients whose life expectancy is less than 10 years.

(2) T1b-c/T2, N0, M0 prostate cancer with a Gleason score ≥ 7 with serum PSA ≤ 20 ng/mL

Active surveillance is not recommended for localized prostate cancer with a Gleason score ≥ 8. Although definitive treatments should be considered if the patient has a life expectancy of at least 10–15 years, no published studies have demonstrated significant survival benefits of any radical therapeutic options in patients with poorly differentiated localized prostate cancer.

(3) T1b-c/T2, N0, M0 prostate cancer with serum PSA ≥ 20 ng/mL

Few published articles have advocated active surveillance for T1b-c/T2 prostate cancer with serum PSA > 20 ng/mL, although PSA alone cannot provide reliable basis for any therapeutic decision. Even under the radiological diagnosis of T1b-c/T2, N0, M0 prostate cancer, the indication for surgery should be considered carefully in the presence of serum PSA > 20 ng/mL, which is a likely sign of more advanced (specifically T3) prostate cancer. In most cases, serum PSA > 100 ng/mL has been associated with distant metastases, which are difficult to control by locoregional therapy alone. Even if initially treated locoregionally, prostate cancer patients with serum PSA > 100 ng/mL are very likely to become candidates for endocrine therapy.

(3) T3, N0, M0 prostate cancer

For T3 prostate cancer definitely indicated radiologically or by digital rectal examination (DRE), radical prostatectomy is not recommended generally because of the high probability of positive surgical margin and microscopic lymph node involvements. Particularly poor outcomes of radical surgery have been reported in patients with T3b prostate cancer (with the involvement of the seminal vesicle). However, findings in the published reports of surgically curable T3 prostate cancer have

reserved prostatectomy as a viable option for some tumors at this stage in those with a life expectancy of at least 10 years. As suggested recently, T3 prostate cancer may be better controlled by irradiation followed by adjuvant endocrine therapy. More evidence is needed to make a definitive statement regarding the optimal treatment of T3 prostate cancer.

(4) T4, N0, M0, N1, or M1 prostate cancer

As prostate cancer at these advanced stages cannot be controlled by locoregional therapy, endocrine therapy should be considered as a first-line treatment, regardless of the life expectancy of the patient.

8. Surgery vs radiation therapy

As mentioned above, two definitive treatment options, radical prostatectomy and radiation therapy, are recommended for localized prostate cancer, and their relative utility is of great interest. A direct comparison between treatments has not been possible, however, owing to the inclusion of different patient populations and the use of different response criteria. The long natural history of the disease, due to its low to medium biological aggressiveness, and the availability of salvage endocrine therapy after failure also prevent a definitive conclusion as to their relative efficacy. A true comparison of the two modalities can only be made possible in a large RCT designed to evaluate overall survival as the primary endpoint in a long-term follow-up. Such an RCT appears impractical in the present medical environment in Japan and there is a question about the validity of data from such an RCT. Even in the presence of overseas such studies that answer this issue it is also questionable whether the results can be extrapolated to Japanese patients.

When conventional radiation techniques have only allowed the delivery of 60–70 Gy, surgery has achieved significantly better outcomes in the treatment of localized prostate cancer. In more recent years, the above-mentioned advancement of radiation techniques has enabled the delivery of higher doses (>70 Gy) as external or interstitial irradiation and has remarkably improved the outcome of radiation therapy. The therapeutic outcome of modern radiotherapy for localized prostate cancer now seems to be as favorable as that of surgery. One of the disadvantages of using radiation as a first-line treatment for localized prostate cancer is that PSA failure following radiation may be an insufficient indicator for salvage surgery, in contrast to the applicability of radiation for postoperative PSA failure. Thus, choice between radiation therapy and surgery may largely depend on the nature and severity of the complications/adverse effects of these modalities. Urinary incontinence and sexual dysfunction are major complications of surgery, while possible adverse effects of radiation on the rectal, micturition and sexual function are of concern. Delayed radiation toxicities and increased risk of secondary cancers after radiotherapy should also be taken into account in deciding the therapeutic strategy for nonelderly patients with prostate cancer.

9. Palliative medicine

(1) Palliative medicine in prostate cancer

While responding to hormonal therapy, even patients with advanced prostate cancer can often remain almost free of severe cancer-related symptoms (e.g. dysuria, hematuria and bone metastatic pain). Once prostate cancer has become refractory to hormones, however, cancer related symptoms also become intractable and unresponsive even to a combination of chemotherapy and hormonal therapy. Thus, most patients with hormone refractory prostate cancer eventually require palliative medicine. Important considerations in palliative medicine for prostate cancer include: (1) how to control bone metastatic pain, (2) spinal paralysis due to spinal metastasis, (3) micturition disorders and hematuria, and (4) postrenal renal failure associated with ureteral obstruction.[170]

(2) Cancer pain relief

Painful bone metastasis presents a therapeutic challenge to practitioners who are treating prostate cancer patients. Many measures are available for the palliation of bone metastatic pain, including analgesics, radiation, corticosteroids, bone-seeking radionuclides, gallium nitrate and bisphosphonates.[171] As analgesics play an important role in cancer pain relief, appropriate analgesic choice is required. According to the World Health Organization (WHO) recommendations, the 'three step ladder' approach is widely used. Briefly, this approach consists of the use of a non-steroidal anti-inflammatory drug (NSAID) at Step 1, combined with the use of a weak opioid and an NSAID at Step 2, and the use of morphine (powder or sustained release formulation) at Step 3. At the last step, the dose of morphine may be escalated according to response, while taking measures for reducing its adverse effects. For further details of the management of cancer related pain, refer to the Evidence-Based Clinical Practice Guidelines for the Management of Cancer Pain (2000), published by the Japanese Society for Palliative Medicine.[172] External beam radiation is very useful for the relief of bone pain in patients with a localized painful bone metastasis[173] (II). For the relief of pain from multiple bone metastases, total or half body radiation has sometimes been used. Recent studies have shown that radioisotopes (e.g. strontium 89) are effective for the osteogenic metastasis of prostate cancer and other malignancies. In RCTs comparing external beam radiation with strontium 89, strontium 89 was as effective as local or half body radiation in relieving existing bone pain and was significantly more effective than local radiation in reducing pain from new bone metastases[174,175] (I). Unfortunately, strontium 89 has not yet been approved in Japan.

Bone metastases of prostate cancer are often osteogenic, characterized by accelerated bone turnover and bone resorption. Because of their ability to inhibit the bone resorptive activity of osteoclasts, bisphosphonates may be useful for the relief of bone metastatic pain and for the prevention of pathological fractures of metastatic bones in prostate cancer patients. An RCT demonstrated that an intravenous bisphosphonate significantly reduced the incidence of complications of bone metastases, including pathological fractures, and was also useful for the relief of bone pain[176] (II). A systematic review has revealed that continued treatment with bisphosphonates since the diagnosis of bone metastasis of prostate cancer significantly reduces the morbidity of bone metastasis, though not affecting the survival of prostate cancer patients with bone metastasis. When bisphosphonates are used for this indication, the intravenous route of administration is preferable to the oral route because bisphosphonates are poorly absorbed from the gastrointestinal tract[177] (I). In Japan, osteoporosis is the only approved indication for oral bisphosphonates, while parenteral formulations of some bisphosphonates have been approved for the management of hypercalcemia due to malignant tumors.

(3) Treatment of spinal paralysis

Treatment options available for the management of spinal paralysis due to spinal metastasis include corticosteroids, radiation therapy and

surgery. Corticosteroid therapy has been used as an adjunct to radiation therapy or surgery and has an established utility for this indication based on data from a RCT[178] (II). However, corticosteroids have caused significant adverse effects and their optimal dose (large or standard dose) for this indication is still controversial. The standard regimen of radiation therapy may be 30 Gy/10 fractions. The most commonly used surgical procedure is spine laminectomy; there is no concern about bone fragility when spinal metastasis of prostate cancer causes spinal paralysis. An RCT comparing radiation therapy alone with spine laminectomy has failed to show any difference in the response rate between the two modalities[179] (II).

(4) Treatment of local symptoms

A recent report suggests that 'palliative' transurethral resection of the prostate (TURP) may be useful for the improvement of micturition disorders in advanced prostate cancer patients and is worthy to be considered for this indication[180] (III). Compared with TURP for benign prostatic hypertrophy, however, palliative TURP for prostate cancer may be more likely to allow the recurrence of urinary retention or may be associated with a greater need for re-operation. Another paper reported that palliative radiation therapy effectively resolved severe hematuria that might cause a tamponade[181] (III).

(5) Measures against hydronephrosis

Urinary obstruction has been reported to occur in 3.3–16% of patients with advanced prostate cancer and seems to be a significant negative prognostic factor in patients with prostate cancer[182] (III). Hydronephrosis resulting from lower urinary tract obstruction due to enlarged prostate cancer is a good indication for urinary catheterization or 'palliative' TURP (see the previous section). Ureteral stenting, ureterocutaneous fistula, or percutaneous nephrostomy (PNS) is indicated for the resolution of ureteral opening stenosis resulting from direct bladder invasion of prostate cancer and for the treatment of hydronephrosis due to ureteral pressurization by lymph node involvement. For patients to be treated with endocrine therapy for non-recurrent prostate cancer, aggressive methods should be used to treat hydronephrosis because their disease is expected to improve, even if transiently. For patients with prostate cancer refractory to hormonal and various other therapies, however, use of PNS for the resolution of hydronephrosis should be considered carefully because of a generally very poor prognosis of refractory prostate cancer[183] (III). Although no RCTs have made comparisons among various therapeutic measures for hydronephrosis (e.g. ureteral stenting, ureterocutaneous fistula and PNS), ureteral stenting or PNS is less invasive than ureterocutaneous fistula. In particular, PNS performed under an ultrasound guide should be considered as a treatment of choice because of its low invasiveness, simple procedure and long life. Ureteral stenting is more convenient for patients but is more likely to allow the recurrence of ureteral obstruction due to malignant tumors[184] (IV).

10. External appraisal of the quality of the 2008 Practice Guidelines for Prostate Cancer

A member of our team (Tomonori Hasegawa, Toho University School of Medicine, Social Medicine Group) appraised the quality of the present Practice Guidelines for Prostate Cancer, using the Appraisal of Clinical Guidelines for Research and Evaluation (AGREE) Instrument. This section presents a description of the internationally standardized appraisal method for the quality of practice guidelines and the results of the appraisal on the quality of the present guidelines.

(1) Evaluation of the quality of clinical guidelines using the AGREE instrument

A checklist devised by a collaborative team for the AGREE was used to assess the quality of the present Practice Guidelines for Prostate Cancer. The AGREE Collaboration devised an internationally standardized assessment frame for the quality of practice guidelines in an attempt to make the smooth creation of guidelines possible, to make it possible for guideline users (government officers, healthcare providers, etc.) to judge which guidelines to use, and to eventually improve the quality of guidelines. This was a collaborative project in which researchers from 12 countries, including the European Union (EU), Canada, and the USA, took part. The AGREE instrument has been recommended by the EU and WHO as an assessment means of practice guidelines.

The AGREE Collaboration has conducted several exploratory researches on clinical guidelines since the middle of 1990s and reported the following findings: (1) Clinical guidelines created in a country/by an organization which has a program for devising clinical guidelines are superior in quality to those created in a country/by an organization which has no such program. (2) A comparison of clinical guidelines created in multiple countries for the same disease indicates that domestic literatures are preferentially cited, and only a few literatures are cited in common by all clinical guidelines created in multiple countries. (3) The contents of recommendations are similar across different countries even when cited literatures differ across countries, suggesting that information is closely communicated among expertise doctors. The results of large-scale clinical studies (so-called mega-studies) and the opinions of leading medical societies are most influential on the contents of recommendations. (4) It is possible to down-scale the checklist for guidelines to some extent, and it is possible to make-up a convenient checklist that enables one to complete the assessment of one set of guidelines in about an hour. However, it still remains unknown whether the quality of the guidelines is improved according to checklist configuration or not.

The current AGREE instrument was designed based on the above-mentioned finding (4). The AGREE instrument has been translated into eight languages and a Japanese version is available.[185] The AGREE instrument has 23 check items in six fields, consisting of a total of 24 check items including one for global assessment. Each check item is rated into one of four classes ranging from 'well fitted = 4 points' to 'not fitted = 1 point' or into the 'no information' class. The point of each check item is summed up by the field. The AGREE instrument is aimed to profile the guidelines and ultimately to show that the guidelines have room for improvement in the fields scoring low points; that is, it is not intended for the summing-up of points in their respective fields to present a global evaluation.

The AGREE instrument consists of the following 23 items in 6 fields: 1. Scope and Purpose: (1) Specific description of the overall objective(s) of the guidelines, (2) Specific description of the clinical question(s) covered by the guidelines, (3) Specific description of patients to whom the guidelines are meant to apply; 2. Stakeholder Involvement: (4) Involvement of representatives from relevant professional groups in the guidelines development group, (5) Consideration of the patient's view and preference, (6) Clear definition of targeted users, (7) Pilot use among targeted users; 3. Rigor of Development: (8) Systematic search for evidence, (9) Clear description of the criteria for selecting the evidence, (10) Clear description of the methods for

formulating the recommendations, (11) Consideration of health benefits, side-effects and risks in formulating the recommendations, (12) Explicit link between the recommendations and the supporting evidence, (13) External review of the guideline prior to publication, (14) Procedure for updating the guidelines; 4. Clarity and Presentation: (15) Specific and unambiguous contents of recommendations, (16) Presentation of different options corresponding to the conditions of patients, (17) Clarity of key recommendations, (18) Availability of tools for the application of the recommendation; 5. Applicability: (19) Potential organizational/regulatory barriers in applying the recommendations, (20) Possible cost implications of applying the recommendations, (21) Presentation of key review criteria for monitoring and audit purposes; 6. Editorial Independence: (22) Description of editorial independence from the funding body, (23) Description of conflicts of interest among the guideline development members. Furthermore, the appraisal of the guidelines as a whole is graded into one of four categories: 'strongly recommended', 'recommended in general (applicable upon a condition or may be modified)', 'not recommended' and 'equivocal'.

(2) AGREE instrument (Japanese version)-based quality assessment of Japanese clinical guidelines

In Japan, since 1999, the formation of clinical guidelines by medical societies has been aided by an MHLW research fund. Moreover, clinical practice guidelines have also often been formulated independently by medical societies. In recent years, about 20 guidelines have been formulated annually in Japan, so the procedure for formulating a set of guidelines may have been substantially established. A total of 53 Japanese clinical guidelines created before 2004 were assessed for their qualities based on the AGREE instrument; the results are presented in Figure 1. Overall, it was indicated that the guidelines formulated more recently have better qualities. It was also suggested that the guideline formulating manner has been markedly improved while Japanese clinical guidelines still have room for improvement with respect to editorial independency and the applicability of recommendations.

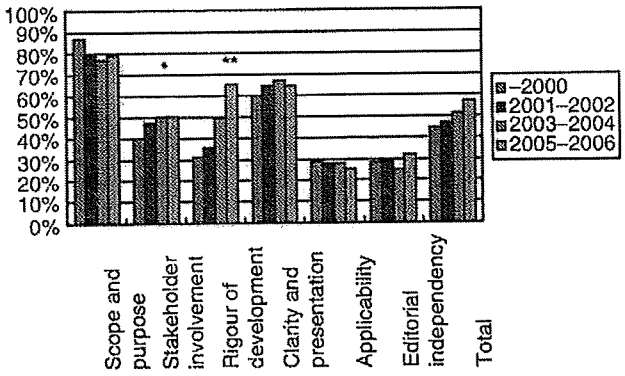

Fig. 1 Results of the Appraisal of Clinical Guidelines for Research and Evaluation (AGREE) instrument-based quality assessment of Japanese guidelines.

(3) Evaluation of the practice guidelines for prostate cancer

The results of the AGREE instrument-based assessment of the Practice Guidelines for Prostate Cancer at the time of proof are presented in Figure 2a, together with the results of the assessments of the above 53 Japanese clinical guidelines. The present guidelines are superior to other Japanese guidelines formed previously with respect to 'rigor of development', 'clarity and presentation', 'applicability', 'editorial independency', and 'total', while it was rather inferior with respect to 'scope and purpose' and 'stakeholder involvement'. Before final editing, the AGREE instrument was delivered to each subgroup of our guideline formulation team so that they might well recognize the assessment criteria. After the final editing, the results of the assessment were greatly improved, as shown in Figure 2b. Since the presence of clear descriptions of specific matters is checked according to the AGREE instrument, the targeted disease and targeted patients, which had before been thought self-evident from the title of the guidelines, were clearly described. It was also clearly described that a number of radiation oncologists and clinical oncologists also participated in the formulation of the present guidelines. These modifications are thought to have resulted in a great improvement in the quality assessment of these guidelines. It is thus emphasized that any clinical guidelines should be formulated in pursuance to the international standardized criteria for the evaluation of clinical guidelines. Further efforts are necessary for the introduction of these clinical practice guidelines to actual healthcare scenes, investigation into the effects of the recommendations on the selection and outcomes of treatment strategy, the review of these guidelines by stakeholders other than urologists and the formulation of commentary from the patients' and their family members' points of view.

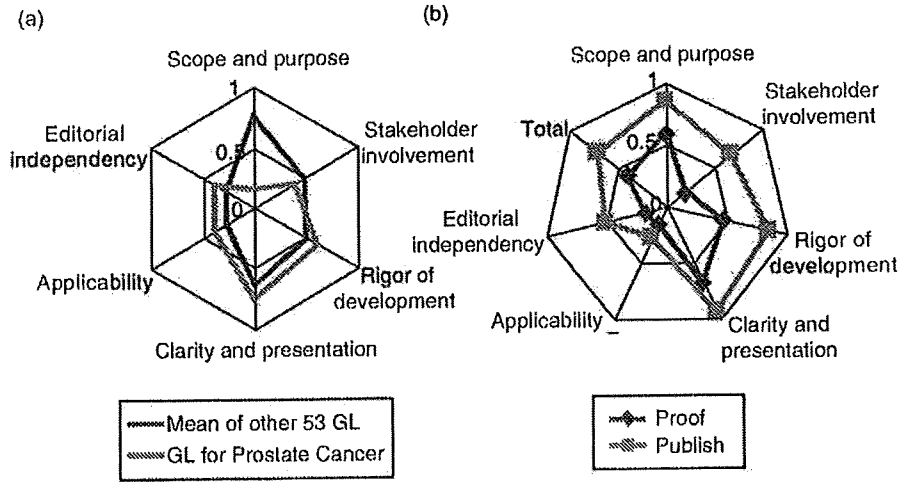

Fig. 2 Results of Appraisal of Clinical Guidelines for Research and Evaluation (AGREE) instrument-based quality assessment of the clinical practice guidelines for prostate cancer versus other Japanese clinical guidelines.

Conclusion

In Japan, the society has been experiencing a prominent expansion of the elderly population in recent years. People are becoming more alert to prostate diseases and prostate cancer has increasingly been arresting social attention.

State-of-the-art advancement has been made to the clinical practices for prostate cancer in Japan, owing to the progress of epidemiological researches associated with the prevalence of local fundamental mass health screening, the promotion of PSA-based minimally invasive diagnosis and the accurate diagnosis associated with the popularization of systematic needle biopsy, and the development and spread of various treatment modalities including surgery, radiation therapy, and pharmacotherapy.

The present Clinical Practice Guidelines for Prostate Cancer have been formulated by the aggregated dedication of the individual members of the Japanese Urological Association as well as the united efforts of the members of the Japan Society of Clinical Oncology and the Japanese Society for Therapeutic Radiation and Oncology, so it is a great fortune of medicine in Japan. Moreover, the present working team pursued precisely the standard processes required for the formulation of the guidelines, as a result of which our society has acquired the know-how for formulating a set of EMB-intended clinical guidelines. This knowledge is a significant resource that can be further utilized for the formulation of guidelines for various diseases in the field of urology as well as future revision of the present guidelines.

The present clinical practice guidelines are believed to be helpful for routine healthcare work, while medicine for prostate cancer is ever-progressing and updated findings are being accumulated every day. The evaluation of the present set of guidelines has already commenced and the process towards the next revision should begin without delay.

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Sensitive detection of *FGFR3* mutations in bladder cancer and urine sediments by peptide nucleic acid-mediated real-time PCR clamping

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Abstract

Somatic mutations of the fibroblast growth factor receptor 3 (*FGFR3*) gene were detected by peptide nucleic acid (PNA)-mediated real-time PCR clamping. Mutation was detected in negative control containing only wild-type DNA due to a misincorporation of dNTPs to PNA binding sites when the amount of template DNA was decreased to 1 ng. Thus, the amount of template DNA was critical determinant of the assay sensitivity in PNA-mediated PCR clamping. Assay conditions were optimized to detect *FGFR3* mutations in exons 7, 10, and 15, at a concentration of more than 1% mutated DNA using 50 ng of genomic DNA as the template. Mutations were detected in 12 of 13 (92.3%) tumor tissues and 11 of 13 (84.6%) urine samples from patients with superficial bladder cancer, while no mutations were detected in tissues and/or urine samples from patients with muscle-invasive bladder cancer or chronic cystitis.

Keywords: Superficial bladder cancer; FGFR3; Mutation; Peptide nucleic acid; Real-time PCR

Bladder cancer is one of the most common malignancies worldwide. In the US, bladder cancer is the fourth most common malignancy in men and the ninth in women; there were some 63,210 new cases in 2005 [1]. Urothelial cell carcinoma (UCC) is a histological subtype accounting for more than 90% of all bladder cancers. Bladder UCCs are generally divided into two groups for clinical management, depending on the pathologic stage. The majority of newly diagnosed UCC is superficial disease (pTa or pT1) and patients are treated by transurethral resection (TUR). However, 50–70% of these patients will experience tumor recurrence and 10–30% will develop muscle-invasive disease (pT2-4) that requires further therapy including cystectomy, chemotherapy or chemoradiotherapy [2]. Cystoscopy is an uncomfortable and invasive examination, but the currently available gold standard for detecting intravesical tumor recurrence. Urine cytology is a noninvasive examination for postoperative management after TUR; however, it is limited by poor sensitivity in cases of low-grade superficial tumors [3].

Recently, mutations of fibroblast growth factor receptor 3 (*FGFR3*) gene have been reported in more than 50% of primary bladder UCC, especially in low-grade and low-stage papillary tumors [2].

Detection of *FGFR3* mutation would be useful for low-grade and low-stage UCCs in urine due to the higher fre-

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