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Guidelines

Japanese clinical practice guidelines for prostate cancer 2023

Yasuo Kohjimoto,[1] Hiroji Uemura,[2] Masahiro Yoshida,[3,4] Shiro Hinotsu,[5] Satoru Takahashi,[6] Tsutomu Takeuchi,[7] Kazuhiro Suzuki,[8] Hiroshi Shinmoto,[9] Tsutomu Tamada,[10] Takahiro Inoue,[11] Mikio Sugimoto,[12] Atsushi Takenaka,[13] Tomonori Habuchi,[14] Hitoshi Ishikawa,[15] Takashi Mizowaki,[16] Shiro Saito,[17] Hideaki Miyake,[18] Nobuaki Matsubara,[19] Norio Nonomura,[20] Hideki Sakai,[21,22] Akihiro Ito,[23] Osamu Ukimura,[24] Hideyasu Matsuyama[25,26] and Isao Hara[1]

[1]Department of Urology, Wakayama Medical University, Wakayama, Japan, [2]Department of Urology and Renal Transplantation, Yokohama City University Medical Center, Yokohama, Kanagawa, Japan, [3]Department of Hepato-Biliary-Pancreatic and Gastrointestinal Surgery, School of Medicine, International University of Health and Welfare, Narita, Chiba, Japan, [4]Department of EBM and Guidelines, Japan Council for Quality Health Care (Minds), Tokyo, Japan, [5]Department of Biostatistics and Data Management, Sapporo Medical University School of Medicine, Sapporo, Japan, [6]Department of Urology, Nihon University School of Medicine, Tokyo, Japan, [7]NPO Prostate Cancer Patients Association, Takarazuka, Hyogo, Japan, [8]Department of Urology, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan, [9]Department of Radiology, National Defense Medical College, Tokorozawa, Tochigi, Japan, [10]Department of Radiology, Kawasaki Medical School, Kurashiki, Okayama, Japan, [11]Department of Nephro-Urologic Surgery and Andrology, Mie University Graduate School of Medicine, Tsu, Mie, Japan, [12]Department of Urology, Faculty of Medicine, Kagawa University, Takamatsu, Kagawa, Japan, [13]Division of Urology, Department of Surgery, Faculty of Medicine, Tottori University, Yonago, Tottori, Japan, [14]Department of Urology, Akita University Graduate School of Medicine, Akita, Japan, [15]QST Hospital, National Institutes for Quantum Science and Technology, Chiba, Japan, [16]Department of Radiation Oncology and Image-Applied Therapy, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [17]Department of Urology, Prostate Cancer Center Ofuna Chuo Hospital, Kamakura, Kanagawa, Japan, [18]Division of Urology, Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan, [19]Department of Medical Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan, [20]Department of Urology, Osaka University Graduate School of Medicine, Osaka, Japan, [21]Department of Urology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [22]Nagasaki Rosai Hospital, Sasebo, Nagasaki, Japan, [23]Department of Urology, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan, [24]Department of Urology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, [25]Department of Urology, Graduate School of Medicine, Yamaguchi University, Ube, Yamaguchi, Japan, and [26]Department of Urology, JA Yamaguchi Kouseiren Nagato General Hospital, Yamaguchi, Japan

Abbreviations & Acronyms
ARSI = androgen receptor signaling inhibitor
CQs = clinical questions
DTX = docetaxel
ICER = incremental cost-effectiveness ratio
JAMS = Japanese Association of Medical Sciences
mCSPC = metastatic castration-sensitive prostate cancer
NND = number needed to diagnosis
NNS = number needed to screen
QALY = quality-adjusted life years
RCT = randomized controlled trials
SRs = systematic reviews

Correspondence
Isao Hara M.D., Department of Urology, Wakayama Medical University, 811-1 Kimiidera, Wakayama 641-8509, Japan.
Email: hara@wakayama-med.ac.jp

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Yasuo Kohjimoto: Guidelines Office of Clinical Practice Guidelines for Prostate Cancer 2023. Isao Hara: Chairman of Working group of Clinical Practice Guidelines for Prostate Cancer 2023.

Abstract: This fourth edition of the Japanese Clinical Practice Guidelines for Prostate Cancer 2023 is compiled. It was revised under the leadership of the Japanese Urological Association, with members selected from multiple academic societies and related organizations (Japan Radiological Society, Japanese Society for Radiation Oncology, the Department of EBM and guidelines, Japan Council for Quality Health Care (Minds), Japanese Society of Pathology, and the patient group (NPO Prostate Cancer Patients Association)), in accordance with the Minds Manual for Guideline Development (2020 ver. 3.0). The most important feature of this revision is the adoption of systematic reviews (SRs) in determining recommendations for 14 clinical questions (CQs). Qualitative SRs for these questions were conducted, and the final recommendations were made based on the results through the votes of 24 members of the guideline development group. Five algorithms based on these results were also created. Contents not covered by the SRs, which are considered textbook material, have been described in the general statement. In the general statement, a literature search for 14 areas was conducted; then, based on the general statement and CQs of the Japanese Clinical Practice Guidelines for Prostate Cancer 2016, the findings revealed after the 2016 guidelines were mainly described. This article provides an overview of these guidelines.

Key words: guidelines, Japan Radiological Society, Japanese Society of Pathology, Japanese Society of Radiation Oncology, Japanese Urological Association, prostate cancer.

INTRODUCTION

Background

In 2006, the first edition of the Clinical Practice Guidelines for Prostate Cancer was published as the first treatment guidelines for malignant tumors related to urology. It covered 114 CQs in seven areas and was created in compliance with the Guide to Developing and Utilizing EBM-Based Clinical Practice Guidelines (2004). Subsequently, the second edition was created in 2012, and the third edition was created in 2016. These treatment guidelines were developed based on the Minds Handbook for Clinical Practice Guideline Development 2007. Since then, new findings in all areas related to prostate cancer, such as disease markers, imaging diagnosis, active surveillance, focal therapy, surgery, radiation therapy, pharmacotherapy, and genomic medicine, have been accumulating one after another; therefore, revision was considered necessary. In 2020, the guideline development group and cooperating committee were selected from the Japanese Urological Association and several other associations and related organizations (Japan Radiological Society, Japanese Society for Radiation Oncology, the Department of EBM and Guidelines, Japan Council for Quality Health Care [Minds], the Japanese Society of Pathology, and the patient organizations [NPO Prostate Cancer Patients Association]) to create the fourth edition in accordance with the Minds Manual for Guideline Development (2020 ver. 3.0) (Chapter 1–4). A major feature of these guidelines was that they incorporated SRs in making recommendations for CQs, and this methodology followed the Minds Manual for Guideline Development (2020 ver. 3.0) (Chapters 1–4). Furthermore, we were joined by Prof. Masahiro Yoshida from the Department of EBM and Guidelines, Japan Council for Quality Health Care (Minds), and Professor Shiro Hinotsu from the Department of Biostatistics and Data Management, Sapporo Medical University School of Medicine, who provided technical guidance. There are two broad types of SRs: quantitative and qualitative. Quantitative SR is commonly referred to as meta-analysis. In a quantitative SR, the actual data from the original papers are combined to statistically calculate the combined value and variability of the effect indicators and their confidence intervals. Initially, we planned to conduct a quantitative SR for some of the CQs; however, many meta-analyses on important themes in the field of prostate cancer have already been published, and our own meta-analysis appears to have little significance. Finally, a qualitative SR for all the CQs was determined. In addition, for the first time, a representative of the patient participated in the guideline development group and identified points that could not have been noticed by the medical staff.

Purpose

Prostate cancer is the most common type of cancer in men, and this trend is expected to continue for some time in Japan as the country continues to age. Prostate cancer is characterized by a wide range of pathologies, ranging from very slow to rapidly progressing. It is therefore not possible to deal with them in a one-size-fits-all manner. In addition, new findings are constantly revealed in both diagnosis and treatment, which requires continuous knowledge updating. These guidelines aimed to promote health in Japan by providing practical clinical guidelines for healthcare providers, patients, and the general public involved in the screening, diagnosis, and treatment of prostate cancer.

Intended users

It is important that the guidelines clearly indicate the intended users. In these treatment guidelines, the intended users are all healthcare professionals involved in the treatment of prostate cancer. Although urologists are the main users, internists, radiodiagnostic physicians, radiotherapy physicians, oncologists, and palliative care physicians are also expected. In addition, the intended users include all healthcare professionals involved in the treatment of prostate cancer, such as nurses, pharmacists, laboratory technicians, and radiology technicians.

The aim of the clinical guidelines is, in particular, to provide recommendations that are considered to be optimal in support of the decision-making process of patients and healthcare professionals. In writing these guidelines, care has been taken to ensure their usefulness for patients with prostate cancer and their families, even though there are likely to be many difficulties. Following the publication of these guidelines, a handbook for patients and the general public will also be developed.

Organizing committee

The Japanese Urological Association and the Japanese Society for Radiation Oncology created the guidelines mainly. In January 2020, a Guideline Committee (Steering Committee) was set up (including the chairman and five other members). The committee held regular meetings in order to discuss the basic policies and the progress made in the creation of guidelines. The guideline development group comprised 24 members, including the guideline steering committee, the directors of the SR and general statement development groups mentioned below, and one patient representative, and votes to decide the recommendations. In these guidelines, 14 CQs were set, and an SR group was formed for each CQ. This was the first time SRs were conducted for urology guidelines; therefore, an SR support group consisting of public health and medical statisticians was set up. Additionally, a general statement development group has been set up to prepare a general statement on 14 areas that cannot be addressed by CQ as textbook descriptions. In addition, an algorithm team was developed to create five algorithms. For external evaluations from a clinical perspective, we primarily asked the External Evaluation Committee of the Japanese Urological Association, members of the Japanese Society for Radiation Oncology, and patient representatives for evaluations.

Clinical questions (CQs)

We picked up issues that were considered important in daily clinical practice and created clinical questions in PICO format (P, patients; I, interventions; C, comparisons and controls; and O, outcomes). Among the proposed 24 questions, we decided to adopt 14 questions after examining their importance and the feasibility of conducting SRs. We then evaluated the importance of each outcome of the selected questions by assigning the 1–9 scores recommended by Minds. After revealing the preliminary scores given by the SR team, the guideline development group members voted to reach a consensus.

Systematic review (SR)

The SR encompasses an extensive investigation of studies relevant to each CQ, grouping the same type of studies based on the research design and conducting analysis and integration while evaluating potential bias. The work was carried out in the following five steps:

1 Evidence collection: For each CQ, the SR team selected approximately 10 keywords and 2 to 3 key papers to set up a query. Comprehensive searches were conducted on PubMed and Igaku Chuo Zasshi (ICHUSHI) from September 1, 2010, to August 31, 2020, based on this query. The search was requested by the Japan Medical Library Association. Papers that were considered necessary but not included in the search results were manually searched and added.
2 Literature screening: As a primary screening, two independent members of the SR team excluded literature that did not align with the CQ content based on the title and abstract of the manuscript. During a second screening, two independent SR team members read the full text of the papers selected during the primary screening to select papers that can extract the outcome related to CQ.
3 Evidence evaluation: The SR team extracted numerical values for each beneficial and harmful outcome of the CQ, evaluated the risk of bias (selection bias, performance bias, detection bias, attrition bias, and other biases), indirectness (differences in study populations, interventions, comparisons, and outcome measurements), and evaluated upgrade factors for observational studies for each adopted paper.
4 Body of evidence evaluation: Based on the evaluation of evidence from each individual paper, the total body of evidence was evaluated for each outcome, including an effect size (large effect, small effect, no effect, inverse effect, and equivalent effect), a summary of the risk of bias, a summary of indirectness, a summary of inconsistency, and a summary of upgrade factors for observational studies. These evaluations determined the strength of evidence for each outcome. The strength of evidence was classified into four levels (strong (A), moderate (B), weak (C), and very weak (D)). If the results of multiple randomized controlled trials (RCTs) or meta-analyses were the same, a strong (A) was given. On the other hand, for observational studies, the evaluation began with a weak (C), and the final judgment was made after taking into account the upgrading and downgrading factors. These results were compiled into a final body of evidence evaluation sheet.
5 Creation of SR reports: A report was composed for each SR based on the above results.

Recommendations development

Based on the results of the SRs, the recommendations development was made and the recommendation was created. Recommendations for an intervention (I) to a patient (P) were decided at four levels: Strongly recommended to do, weakly recommended to do, weakly recommended not to do, and strongly recommended not to do. Specifically, based on the evaluation of each outcome conducted in the SRs, the magnitude and certainty of the beneficial outcomes and harmful outcomes were closely examined and assessed. Additionally, the values, preferences, burden of patients (for CQ2, for instance, how widely MRI is used in Japan, how much it is accepted by the general public, and how invasive is MRI?), and cost and resource use (costs associated with MRI examination, cost burden for patients, etc.) were also taken into consideration in deciding the final recommendation.

The SR team assigned to each CQ prepared a draft of the recommendation and voted on by the guideline development group. Recommendation decision meetings took place via a web conference on April 27, and May 6, 2022. Members with financial or academic COI did not vote on the relevant questions. The strength of the recommendation was determined based on the voting results, following the criteria listed below:

1 If more than 80% of the votes were “highly recommend,” it will be seen as “highly recommended.”
2 If condition (1) is not met, but more than 80% of the votes concentrate in a particular direction, it will be seen as “weakly recommended.”
3 If neither condition (1) nor (2) above is met, discuss the results publicly and vote again.
4 If no decision can be made after repeating this process three times, there will be “no recommendation.”

For 2 of the 14 CQs, it was extremely difficult to decide on a recommendation based on the SRs’ results; hence, from the first round of voting, the option of “no recommendation” was set.

CLINICAL QUESTIONS AND RECOMMENDATIONS

CQ1: Is PSA screening for prostate cancer in middle-aged men recommended?

Recommendation: PSA screening for prostate cancer should be proposed for men aged 50 years and older because of the potential to reduce mortality and metastasis. However, providing information on the risk–benefit analysis and following the individual’s wishes is preferable.

[Level of recommendation: recommended; Strength of Evidence: B (moderate)] (Tables 1 and 2).

Background

Prostate cancer cases and deaths in Japan are on the rise. Because the physical and mental burden on patients with metastases is significant, evaluation of the effectiveness of prostate cancer screenings is a critical clinical issue based not only on reduced mortality rates but also on benefit–harm analysis and the extending effect on quality-adjusted life years (QALY). Furthermore, when implementing cancer screenings on a national level, it is essential to evaluate them from an economic perspective in healthcare.

Literature search

A comprehensive literature search yielded 401 papers. A total of 41 papers were selected after screening. Thirteen were randomized controlled trials (RCTs), 21 were observational studies, 1 meta-analysis, and 6 reviews.

SR results

O1: Decrease in all-cause mortality: There is no risk of bias as all deaths are considered an outcome; no effect has been proven in intervention studies,[1–3] and there is no inconsistency among studies. Therefore, the intervention was evaluated as "No effect" on O1, and the strength of evidence was rated B (medium). However, a reduction in all-cause mortality is not appropriate as the primary endpoint when evaluating the effectiveness of cancer screening in healthy individuals. If there is no difference in all-cause mortality, it means that there is no bias in background factors between the screening group and the control group.

O2: Decrease in cancer mortality: In a qualitative systematic review of 29 articles, the ERSPC[4] intervention study, which has little execution bias, case reduction bias, and other biases, proved a significant about 20% cancer mortality rate decreasing effect among 55- to 69-year-olds through intention-to-screen (ITS) analysis. Similarly, in the Göteborg study,[5] an intervention study where the risk of such biases is very low; a large 44% drop in cancer mortality rate was demonstrated through ITS analysis during a median observation period of 14 years. Considering that these are high-confidence intervention studies with a low bias risk, which could demonstrate a relatively large reduction in cancer mortality rate, and that there are no high-confidence intervention studies, SRs, or observational studies that do not acknowledge the effect of reducing the cancer mortality rate, the intervention was evaluated to have a "Large effect" on O2. Taking into account the fact that the number of highly reliable studies is somewhat small and the research is done overseas; the strength of evidence was rated as B (moderate).

O3: Decrease in metastatic cancer incidence: Studies with low-risk bias and high reliability[6,7] have demonstrated a considerable reduction in metastatic cancer. As there is no inconsistency among studies, the intervention is evaluated as having a "Large effect" on O3, and the strength of evidence is regarded as A (strong).

O4: Increase in complications: Examining complications due to anxiety from participating in screening, prostate biopsy-related complications, and complications such as urinary incontinence and erectile dysfunction, in the examination occasion treatment group, the intervention is considered to have a "Small effect" on O4. Some RCTs[6,8] do not reach the same conclusion; hence, the strength of evidence is C (weak).

O5: Increase in overdiagnosis and overtreatment: Due to intervention by testing, there is a corresponding increase in overdiagnosis.[9–11] The intervention is therefore considered to have a "Large effect" on O5. However, it is currently limited to model analysis and has not yet reached an analysis in the real world using large-scale RCTs. Therefore, the strength of evidence is B (moderate).

O6: Excess cost: Many reports indicate that testing will increase excess costs by about 5000 JPY. The intervention is evaluated as having a "Small effect" on O6. While centered on

TABLE 1 Committee vote results of CQ1.

Strongly recommended	Weakly recommended	Weakly recommended not to do	Strongly recommended not to do
1 (5%)	19 (95%)	0 (0%)	0 (0%)

TABLE 2 Components of the CQ1: P (Patients): Middle-aged male; I (Interventions): PSA testing intervention; C (Comparisons, Controls): No PSA screening; O (Outcomes): (see below).

	Outcome	Benefit/harm	Importance (points)	Effect of intervention on outcome	Strength of evidence
O1	Decrease in all-cause mortality	Benefit	4	No effect	B (Moderate)
O2	Decrease in cancer mortality	Benefit	9	Large effect	B (Moderate)
O3	Decrease in metastatic cancer incidence	Benefit	8	Large effect	A (Strong)
O4	Increase in complications	Harm	6	Small effect	C (Weak)
O5	Increase in overdiagnosis and overtreatment	Harm	8	Large effect	B (Moderate)
O6	Excess costs	Harm	7	Small effect	C (Weak)
O7	Extension of quality-adjusted life years (QALY)	Benefit	6	Small effect	C (Weak)
O8	Testing efficiency (ICER, NNS, and NND)	Benefit/harm	6	Small effect	C (Weak)

simulation model analysis under various assumptions,[9–14] integration is difficult; hence, the strength of evidence is C (weak).

O7: Extension of quality-adjusted life years (QALY): There are many reports suggesting that testing will slightly increase QALY.[10,12–14] Thus, O7 is rated as having a "Small effect," but due to difficult integration in simulation model analysis, the strength of evidence is C (weak).

O8: Testing efficiency (incremental cost-effectiveness ratio (ICER), number needed to screen (NNS), and number needed to diagnosis (NND)): Many prerequisites are needed to keep the ICER, the cost required to gain one unit of QALY, in the optimal range,[10] and such prerequisites include age restriction and popularization of active surveillance. Efficiency comparable to other types of screening is also suggested for NNS,[1,5] but direct comparisons are difficult. Therefore, the intervention is rated as having a "Small effect" on O8 and the strength of evidence is C (weak) due to primarily being based on simulation model analysis.

Balance between benefits and harms

When PSA screening is offered to healthy men, beneficial outcomes, such as decreases in the cancer mortality rate (O2) and the metastatic cancer rate (O3), can be expected. However, it may also lead to unfavorable outcomes, such as an increase in complications (O4), as well as overdiagnosis and overtreatment (O5). Because the two beneficial outcomes directly impact life expectancy, they are highly significant and are also highly credible as strength of evidence. Furthermore, although it may be difficult to conduct studies with strong evidence on QALY extension (O7), which is another significant outcome, benefits can still be expected. Healthy men are considered subjects for screening; hence, it is essential to provide them with information about both benefits and harms. Despite the presence of harms, since the benefits outweigh the harms, we have proposed the implementation of PSA testing for men over 50 years of age.

Values, preferences, and burden of patients

There is a wide range of individual differences in the public's attitudes toward prostate cancer screening, so when implementing screening, it is important to provide information using fact sheets, etc., about the effects of decreased metastatic cancer incidence, reduced cancer mortality, and extended QALY, and the benefits and harms. It is desirable to implement prostate cancer screening according to each individual's intentions through shared decision-making.

Cost and resource use

The cost of PSA screening is not a significant financial burden for each individual recipient, as it is fully or partially borne by local governments. The cost of cancer diagnosis and treatment, including follow-up, is all performed under insured services, so there is no risk of unexpected patient resource investment.

Recommendations development

The benefits outweigh the harms, and after going through the process of shared decision-making, the idea of the testing is well received. There also seems to be no problem from the perspective of cost and resource use. The overall evaluation of the strength of evidence was B, and as 95% of votes were for proposing the implementation of the testing, the recommendation was finalized.

CQ2: Are MRI scans recommended before biopsy in patients with high PSA levels?

Recommendation: MRI scans before a biopsy are weakly recommended in patients with high PSA levels.

[Level of Recommendation: Weak recommendation; Strength of Evidence: C (Weak)] (Tables 3 and 4).

Background

Patients with high PSA levels are often diagnosed with prostate cancer through a transrectal ultrasonography-guided systematic biopsy. Recently, it has been shown that performing multiparametric MRI prior to biopsy and conducting target biopsy for only those patients with positive MRI findings increase detection of clinically significant cancers and decrease detection of clinically insignificant cancers, thus avoiding unnecessary biopsies. The question of whether MRI prior to biopsy is recommended compared to performing the biopsy without MRI was discussed.

Literature search

A comprehensive literature search yielded 751 articles. After the first screening, 718 articles were ruled out, and in the second screening, using the main criteria of "increase in detection of clinically significant cancer" and "decrease in detection of clinically insignificant cancer," which are the important outcomes for this CQ, a total of 11 articles were finally selected.[15–25] The 11 articles include three randomized controlled trials (RCT), 4 meta-analyses, and 4 prospective cohort studies.

SR results

O1: Increase in detection of clinically significant cancer: According to the results of an RCT by Panebianco et al., which involved 1140 patients with elevated PSA levels (>4 ng/mL), the detection rate of clinically significant cancer was 39% among the 570 patients who underwent a 3 Tesla MRI scan. This was significantly higher than the 31% detection rate among the 570 patients who did not have an MRI scan.[19] Similarly, 9 of the 10 studies reported that the detection rate of clinically significant cancers was higher in the group that had a prebiopsy MRI compared with the systematic biopsy group. Based on these findings, the intervention

TABLE 3 Committee vote results of CQ2.

Strongly Recommended	Weakly recommended	Weakly recommended not to do	Strongly recommended not to do
1 (5%)	19 (95%)	0 (0%)	0 (0%)

TABLE 4 Components of the CQ2: P (Patients): Patients with high PSA levels; I (Interventions): MRI scan before biopsy; C (Comparisons, Controls): No MRI scan before biopsy; O (Outcomes): (see below).

	Outcome	Benefit/harm	Importance (points)	Effect of intervention on outcome	Strength of evidence
O1	Increase in detection of clinically significant cancer	Benefit	9	Large effect	B (Moderate)
O2	Decrease in detection of clinically insignificant cancer	Benefit	7	Small effect	C (Weak)
O3	Decrease in biopsy complications (adverse events)	Benefit	6	Small effect	C (Weak)
O4	Increase in medical costs	Harm	6	No effect	D (Very Weak)
O5	Increase in MRI complications (adverse events)	Harm	4	Small effect	C (Weak)

was evaluated as having a "large effect" on O1. However, considering that the analysis includes observational studies and studies with bias and that one RCT reported equal detection rates for both groups, the strength of evidence was assessed as B.

O2: Decrease in detection of clinically insignificant cancer: In a large prospective cohort study of 740 patients by Ahmed et al., it was demonstrated that the detection of clinically insignificant cancer was reduced by 5% through triage by multiparametric MRI.[24] However, in an RCT by Tonttila et al. involving 130 patients with high PSA levels, the detection rate of clinically insignificant cancer was 9.4% in the 53 cases where MRI was performed before biopsy, and 12% in the 60 systematic biopsy cases, with no significant difference in the detection rate of clinically insignificant cancer between the two groups.[20] Of the seven papers examined, three papers showed a significant decrease in the detection rate of clinically insignificant cancer in the group that received an MRI before the biopsy compared with the systematic biopsy group; however, no such significant difference was observed in the four papers. As for decrease in the detection of clinically insignificant cancer, consistent data could not be obtained; therefore, the intervention was judged to have a "Small effect" on O2, and the strength of evidence was judged as C.

O3: Decrease in biopsy complications (adverse events): There is only one paper on O3, which reported that in a comparison between the multiparametric MRI + targeted biopsy group and the systematic biopsy group, the frequency of hematuria was 30% versus 63%, hemospermia 32% versus 60%, rectal bleeding 14% versus 22%, erectile dysfunction 11% versus 16%, and pain at the treatment site 13% versus 23%.[25] The frequency of biopsy complications was lower with the MRI route, but since only one paper was extracted and there might be bias, the intervention was judged to have a "Small effect" on O3, and the strength of evidence was judged as C.

O4: Increase in medical costs: With regard to O4, both of the two examined papers[19,26] are overseas studies and do not directly apply to Japan. Therefore, the intervention was judged to have "No effect" on O4, and the strength of evidence was assessed as D.

O5: Increase in MRI complications (adverse events): As for O5, one prospective cohort study by Ahmed et al., targeting 740 cases, was available for evaluation.[24] Reports after the MRI test included the occurrence of side effects, such as pain and discomfort in 11 cases, allergic reactions to contrast agents in 1 case, and other events in 3 instances. As there was only one paper to examine, the intervention was judged to have a "Small effect" on O5, with the strength of evidence assessed as C.

Balance between benefits and harms

For patients with high PSA levels, "the increase in detection of clinically significant cancer" (O1), "the decrease in detection of clinically insignificant cancer" (O2), and "the decrease in biopsy complications (adverse events)" (O3) by MRI scan prior to biopsy are considered "beneficial" outcomes. On the other hand, "the increase in medical costs" (O4) and "the increase in MRI complications (adverse events)" (O5) are considered harmful outcomes for the patients. The beneficial outcomes have larger effects and higher strength of evidence compared with the harms, so the benefits were judged to outweigh the harms.

Values, preferences, and burden of patients

MRI examinations are widely accepted, and it is thought that there is little variation in patient opinions regarding undergoing an MRI scan prior to prostate biopsy. Although the medical expenses are a burden, there is no radiation exposure, and it is thought to be acceptable as something that matches the net benefit, such as an increase in the detection of clinically significant cancers, and has the potential to avoid complications of prostate biopsies.

Cost and resource use

In Japan, although there are issues with the efficiency of equipment usage, the pervasiveness of MRI scanners per capita is relatively advanced, and prostate MRI examination covered by insurance is a relatively easy option for patients, meaning that the amount required to be paid by patients is not that high.

Recommendations development

The benefits outweigh the harms, public acceptance is favorable, and there are no problems from the perspective of cost

and resource use. Overall evaluation of the strength of evidence was assessed as C, and it was judged to be "Weakly recommend" on the basis of 80% or more of the votes.

CQ3: Is it recommended to omit contrast-enhanced MRI in the MRI diagnosis of primary prostate cancer?

Recommendation: Contrast-enhanced MRI can be omitted in the MRI diagnosis of primary prostate cancer. However, it is desirable to have facilities where optimized examinations are performed with a 3 Tesla MRI machine, experienced radiologists evaluate the images, and pathological diagnosis can be made by biopsy guided by the MRI information.

[Level of Recommendation: Weak recommendation; Strength of Evidence: C (Weak)] (Tables 5 and 6).

Background

The usefulness of MRI in the localization of prostate cancer is widely known. In recent years, the role of dynamic contrast-enhanced imaging has declined and become more limited since the advent of PI-RADS version 2, a standardized evaluation method using multiparametric MRI (mpMRI: T2-weighted imaging, diffusion-weighted imaging, and dynamic contrast-enhanced imaging). There are also reports that biparametric MRI (bpMRI), which only uses T2-weighted imaging and diffusion-weighted imaging for the diagnosis, has a comparable diagnostic performance to mpMRI. Therefore, we investigated in the literature whether bpMRI is not inferior in terms of diagnostic accuracy of clinically significant cancers compared with mpMRI.

Literature search

A comprehensive literature search extracted 332 papers, from which 18 papers were ultimately selected. Among them, papers regarding O1 and O2 were deemed impossible to evaluate for bias risk, so we conducted a qualitative systematic review of the 14 papers for O3,[27–40] and the 3 papers for O4.

TABLE 5 Committee vote results of CQ3.

Strongly recommended	Weakly recommended	Weakly recommended not to do	Strongly recommended not to do
0 (0%)	17 (85%)	3 (15%)	0 (0%)

SR results

O3: Decrease in diagnostic accuracy of clinically significant cancer: All 14 papers examined were observational studies.[27–40] The histopathological evaluation (reference standard) for prostate cancer was performed by MRI-guided prostate biopsy (mainly MRI-ultrasound fusion-guided biopsy), total prostatectomy, or detailed template biopsy. Image evaluations were carried out by experienced radiologists in all papers except for one. Most of the MRI examinations were performed using a 3 Tesla device. Among the comparisons of mpMRI and bpMRI, significant differences in detection ability were identified in only 2 of 14 papers[31,35]; (bpMRI had lower sensitivity and higher specificity than mpMRI). Thus, we concluded that the decrease in the accurate diagnosis rate for clinically significant cancers with bpMRI is uncertain, and the intervention was judged to have "No effect" on O3. Also, as all papers were observational studies, the strength of evidence was rated as C (weak).

O4: Decrease in detectability of posttreatment recurrent tumors: All three papers evaluated were observational studies. These papers were compilations of studies with different treatments (radiation therapy, total prostatectomy, and high-intensity focused ultrasound (HIFU)). Therefore, there was a lack of evidence to determine the strength of the recommendation, and we made this outcome a future research question. The strength of evidence was rated as D (very weak).

Balanced assessment of benefits and harms

When using bpMRI without contrast-enhanced MRI instead of mpMRI, the benefits of "cost reduction" and "reduction in the incidence of side effects" are certain. Furthermore, the diagnostic capability of primary clinically significant cancer using bpMRI was found not to be inferior to mpMRI. Therefore, it was determined that the overall benefits outweigh the harm.

Values, preferences, and burden of patients and citizens

In facilities where inappropriate MRI image acquisition and artifact countermeasures, MRI diagnosis by experienced

TABLE 6 Components of the CQ3: P (Patients): Patients suspected to have prostate cancer (primary/local recurrence); I (Interventions): Biparametric MRI (bpMRI) (non-contrast-enhanced MRI); C (Comparisons, Controls): Multiparametric MRI (mpMRI) (contrast-enhanced MRI); O (Outcomes): (see below).

	Outcome	Benefit/harm	Importance (Points)	Effect of Intervention on Outcome	Strength of evidence
O1	Decrease in medical expenses	Benefit	5	Not assessable	Not assessable
O2	Decrease in examination complications (adverse events)	Benefit	6	Not assessable	Not assessable
O3	Decrease in diagnostic accuracy of clinically significant cancer	Harm	8	No effect	C (Weak)
O4	Decrease in detectability of posttreatment recurrent tumors	Harm	7	Small effect	D (Very Weak)

radiologists, and appropriate pathological diagnosis are available, the clinical application of bpMRI, which is comparable to mpMRI in diagnostic ability for clinically significant cancers, is expected to reduce examination time and the risk of side effects of contrast media. Therefore, it is thought that the clinical application of bpMRI will be accepted by most patients due to the benefits that it affords.

Cost and resource use

Compared with mpMRI, bpMRI, which does not involve contrast-enhanced MRI, will certainly decrease the patient's share of medical expenses.

Recommendations development

It was thought that the benefits outweigh the harm, patient and citizen acceptance is expected to be good, and there is no problem from the perspective of cost and resource use. However, the strength of evidence is rated C (weak), and the proposal was made to "Weakly recommend" for bpMRI. It was finalized with over 80% of the votes.

CQ4: Is personalized treatment based on genomic diagnosis recommended for patients with metastatic castration-resistant prostate cancer (mCRPC)?

Recommendation: Personalized treatment based on genomic diagnosis is useful for patients with mCRPC. However, cases that lead to effective drug selection are limited at this point. Therefore, it is weakly recommended to perform genomic diagnosis depending on the patient's request.

[Level of Recommendation: Weak recommendation; Strength of Evidence: C (Weak)] (Tables 7 and 8).

Background

Olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, is expected to have an antitumor effect if there are germline or somatic pathogenic variants in *BRCA1/2*, which play a crucial role in DNA repair. There is a demand for personalized treatments based on such genomic diagnosis. We investigated whether this personalized medicine based on genomic diagnosis is recommended.

TABLE 7 Committee vote results of CQ4.

Strongly recommended	Weakly recommended	Weakly recommended not to do	Strongly recommended not to do
1 (5%)	16 (80%)	3 (15%)	0 (0%)

Literature search

A comprehensive literature search found 369 papers and 21 papers were hand searched. As a result of screening, 4 papers with a high level of evidence were selected. All of them were about olaparib, a PARP inhibitor.

SR results

O1: Extension of overall survival: The results of the PROfound trial showed the usefulness of olaparib, a PARP inhibitor, in extending the overall survival period for mCRPC (cohort A) with any genetic variant (pathological variant) of *BRCA1*, *BRCA2*, or *ATM* when compared with enzalutamide or abiraterone plus prednisone.[41] However, the PROfound trial is the only evidence, and the number of Japanese cases enrolled was small. Therefore, caution is required in interpreting the results. Hence, O1 (extension of overall survival, benefit/importance 9 points) is evaluated as having a "Large effect," but considering the small number of high-quality studies and that the majority of the cases are non-Japanese, the strength of evidence is rated B (moderate).

O2: Extension of progression-free survival: The results of the PROfound trial showed the usefulness of olaparib, a PARP inhibitor, in extending the progression-free survival period for mCRPC with any genetic variant (pathological variant) of *BRCA1*, *BRCA2*, or *ATM* when compared with enzalutamide or abiraterone plus prednisone.[42] However, the PROfound trial is the only evidence, and the number of Japanese cases enrolled was small. Therefore, caution is required in interpreting the results. Hence, the intervention was judged to have a "Large effect" on O2 (extension of progression-free survival, benefit/importance 8 points), but considering the small number of high-quality studies and that the majority of the cases are non-Japanese, the strength of evidence was rated B (moderate).

O3: Adverse events from medication: Based on the results of the Phase II TOPARP-A trial and the Phase III PROfound trial for olaparib, it is possible that events such as anemia, nausea, and diarrhea may occur as adverse events associated with the use of olaparib.[43] However, no statistical analysis has been conducted on the frequency of adverse events, and no significant difference has been demonstrated with the control group. Therefore, the intervention was judged to have a

TABLE 8 Components of the CQ4: P (Patients): Patients with mCRPC; I (Interventions): Personalized treatment based on genomic diagnosis; C (Comparisons, Controls): Treatment without genomic diagnosis; O (Outcomes): (see below).

	Outcome	Benefit/harm	Importance (points)	Effect of intervention on outcome	Strength of evidence
O1	Extension of overall survival	Benefit	9	Large effect	B (Moderate)
O2	Extension of progression-free survival	Benefit	8	Large effect	B (Moderate)
O3	Adverse events from medication	Harm	7	Small effect	C (Weak)
O4	Cost burden of genomic diagnosis	Harm	7	Small effect	C (Weak)

"Small effect" on O3 (adverse events of drugs, harm/importance 7 points), and the strength of evidence is rated C (weak).

O4: Cost burden of genomic diagnosis: Based on the results of the PROfound trial, it is estimated that about 20% of patients are suitable for olaparib. In Japan, there is no concrete data on mCRPC patients with *BRCA1* or B*RCA2* genetic variants, but assuming that the proportion is the same in Japan, the incidence of cases suitable for olaparib is estimated to be about 20%.[42] Therefore, even if a genomic profiling test is performed, it is not sufficient to be considered "personalized medicine" as few can access the drug. The cost of a genomic test is also substantial. Furthermore, the frequency of cases suitable for olaparib based on genomic diagnosis is estimated based on the results of foreign clinical trials. Therefore, the intervention was judged to have a "Small effect" on O4 (cost burden of genomic diagnosis, harm/importance 7 points), and the strength of evidence is rated C (weak).

With regard to this CQ, the important outcomes are O1, O2, O3, and O4. The strength of evidence for O1 and O2 is B, and for O3 and O4, it is C; hence, the overall evaluation is determined as C.

Balance between benefits and harms

The beneficial outcomes of personalized treatment based on genomic diagnosis in mCRPC are "extension of overall survival" (O1) and "extension of progression-free survival" (O2), both of which are considered desirable effects for patients. On the other hand, the harms, namely "adverse events from medication" (O3) and the "cost-burden of genomic diagnosis" (O4), are undesirable effects for patients. However, since the beneficial outcomes have large effects and strong evidence, we have recommended personalized treatment based on genomic diagnosis for mCRPC. However, since only a limited number of cases lead to effective drug selection and there is a lack of basis and benefits for recommending genomic diagnosis to all mCRPC patients at the present time, we have added the term "as per the patient's request."

Values, preferences, and burden of patients

Olaparib, a PARP inhibitor, is expected to be effective in mCRPC cases with pathogenic variants of *BRCA1/2* identified through genomic diagnosis. However, only about 20% of cases are present with *BRCA1/2* gene variants.[42] The only drugs known to be effective against other gene variants are immune checkpoint inhibitors (pembrolizumab) at this point, and even then, they can only be expected to be effective in 2%–3% at most. However, considering things from the patient's perspective, offering a glimmer of hope in a situation where there are no other treatment options would seem to be worthwhile to perform a genomic diagnosis if the patient so wishes. Conversely, when secondary findings are identified through genomic diagnosis, there is also the potential benefit of preventing diseases that the patient or the family might develop in the future. However, there are concerns about the mental distress associated with genomic diagnosis.

Cost and resource use

In cases of mCRPC that have relapsed after new hormone therapy, if a genomic diagnosis reveals pathological variants of *BRCA1* or *BRCA2*, the drug olaparib, a PARP inhibitor, is now covered by insurance. However, patients should be informed that olaparib is an expensive medication.

For the purpose of genomic diagnosis, patients must undergo testing and expert panel judgment of test results at a core hospital for cancer genomic medicine or base hospital for cancer genomic medicine, using either FoundationOne® CDx on tumor tissue or Foundation-One® Liquid CDx on circulating tumor DNA in the blood. Both types analyze mutations in 324 cancer-related genes. FoundationOne® CDx can provide information on microsatellite instability (MSI) and tumor mutation burden (TMB), while Foundation-One® Liquid CDx cannot. The former also allows for both morphological and molecular evaluation, while the latter captures the heterogeneity of genomic information in tissue samples and enables profiling representing the whole body condition. It should be noted that this is 56 000 points under insurance, leading to a great financial burden for patients. Meanwhile, BRACAnalysis® using white blood cells from blood for companion diagnosis of olaparib has a lower hurdle, as there are no restrictions on the facilities performing testing as long as a system for genetic counseling is in place. However, it can only identify germline variants, and there is a chance that it may miss somatic variants of *BRCA1/2* that are commonly seen in prostate cancer. Furthermore, this test is 20 200 points under insurance, resulting in a high medical cost for patients. These aspects must be fully explained to patients, and the test must be performed only with patient consent.

If the result of the BRACAnalysis® is negative, it is possible to carry out a cancer genomic profiling test using FoundationOne® CDx or Foundation-One® Liquid CDx after the disease progresses to search for somatic variants. However, this incurs an additional 56 000 insurance points, leading to an additional financial burden for the patient, which must be made known upfront.

When using FoundationOne® CDx or FoundationOne® Liquid CDx for olaparib companion diagnosis, this would be 20 200 insurance points, the test will be conducted after disease progression, and the results will be presented after being reviewed by an expert panel. However, at this stage, opportunities to administer effective drugs within the scope of treatments covered by insurance are extremely limited for cases without *BRCA1/2* variants. Thus, patients may not request a cancer genomic profiling evaluation when their condition has already progressed. In situations where patients do not request presentation of cancer genomic profiling test results, even if FoundationOne® CDx or FoundationOne® Liquid CDx is 56 000 insurance points, the difference of 35 800 points (56 000–20 200) cannot be billed to the patient. In such a case, the medical institution implementing the test will have to bear the cost. Therefore, as of now, using FoundationOne® CDx or FoundationOne® Liquid CDx for companion diagnosis of olaparib is not the ideal testing procedure, and it is hoped this situation can be improved in the future.

Recommendations development

The benefits outweigh the harms, and the public accepts it well. However, from a cost and resource use perspective, improvements in the companion diagnostic method are desired in the future. Due to a combined evaluation of the level C strength of evidence, it was proposed to "Weakly recommend" the intervention, which was agreed upon by more than 80% of the voters.

CQ5: Is active surveillance recommended for intermediate-risk prostate cancer?

Recommendation: Active surveillance is weakly recommended for patients with intermediate-risk prostate cancer who meet all of the following conditions: Gleason score of 3 + 4 or less, positive core number of 2 or less, PSA 10 ng/mL or less, PSA density (PSAD) less than 0.2 ng/mL/mL, and not including cribriform or intraductal carcinoma.

[Level of Recommendation: Weak recommendation; Strength of Evidence: C (Weak)] (Tables 9 and 10).

Background

Active surveillance for low-risk prostate cancer is established as one of the standard treatments. Can this be expanded to include intermediate-risk prostate cancer? The NCCN guidelines divide intermediate risk into "favorable" and "unfavorable" and further determine the appropriateness of active surveillance based on life expectancy. Its validity needs to be verified.

Literature search

With regard to this CQ, 403 papers related to active surveillance for intermediate-risk prostate cancer were extracted. We excluded 388 papers in the first screening and conducted a second screening on 15 papers. We primarily focused on the therapeutic outcomes of active surveillance for intermediate-risk prostate cancer among the major outcomes related to this CQ, which are "reduction of medical expenses," "reduction of side effects from radical treatment," "loss of opportunity for cure," and "increase in prostate cancer mortality rate," and then reviewed the results of nine papers.

TABLE 9 Committee vote results of CQ5.

Strongly recommended	Weakly recommended	Weakly recommended not to do	Strongly recommended not to do
0 (0%)	17 (89.5%)	2 (10.5%)	0 (0%)

SR results

O1: Decrease in medical expenses: No articles were found that discussed the effect of reducing medical costs through active surveillance for intermediate-risk prostate cancer. Therefore, an evaluation regarding the reduction of medical costs could not be performed. Consequently, O1 could not be evaluated, and the strength of evidence was rated as "not assessable."

O2: Decrease in side effects from radical treatment: One of the objectives of active surveillance is to avoid the side effects associated with radical treatment. "Reduced side effects" brought about by active surveillance were evaluated on the basis of treatment-free survival rates.

Nine studies discussed the treatment-free survival rate on active surveillance that included intermediate-risk prostate cancer.[44–52] The treatment-free survival rates of intermediate-risk cases in each study for 5, 10, and 15 years were 49%–73.5%, 41%–69%, and 13%–49%, respectively. Although the treatment-free survival rate decreases over the years and a transition to subsequent treatment can be observed, it was considered that the objective of active surveillance to avoid overtreatment seems achieved in the short term, and the intervention was judged to have a "Large effect" on O2. However, since all the studies were single-arm observational studies, the strength of evidence was rated C.

O3: Loss of opportunity for cure: There are cases in which metastasis can occur during active surveillance, making it impossible to choose radical therapy. The "loss of opportunity for cure" by active surveillance was evaluated based on the metastasis-free survival rate. There were six articles that mentioned the metastasis-free survival rate in research on active surveillance that included intermediate-risk prostate cancer,[44,47,48,50–52] and the metastasis-free survival rate for intermediate-risk prostate cancer was 98%–99% (5 years), 91%–100% (10 years), and 82%–100% (15 years). Looking at the long term, up to 20% of cases showed metastases, and the intervention was judged to have a "Small effect" on O3. However, since all the studies were single-arm observational studies, the strength of evidence was rated C.

TABLE 10 Components of the CQ5: P (Patients): Intermediate-risk prostate cancer patients; I (Interventions): Active surveillance; C (Comparisons, Controls): Immediate radical treatment (surgery/radiation); O (Outcomes): (see below).

	Outcome	Benefit/harm	Importance (points)	Effect of intervention on outcome	Strength of evidence
O1	Decrease in medical expenses	Benefit	6	Not assessable	Not assessable
O2	Decrease in side effects from radical treatment	Benefit	8	Large effect	C (Weak)
O3	Loss of opportunity for cure	Harm	8	Small effect	C (Weak)
O4	Increase in cancer mortality rate	Harm	9	Small effect	C (Weak)

O4: Increase in prostate cancer mortality rate: The "increase in prostate cancer mortality" due to active surveillance was evaluated based on the cancer-specific survival rate. There were nine articles that mentioned the cancer-specific survival rate,[44–52] and the cancer-specific survival rate for intermediate-risk prostate cancer was 100% (5 years), 96.1%–100% (10 years), and 89%–100% (15 years). In long-term follow-up, cancer deaths were observed in up to 11% of cases, and as some reports suggest that the 10-year cancer-specific mortality rate for active surveillance is higher than that of surgery or radiotherapy,[53] the intervention was judged to have a "Small effect" on O4. However, since all the studies were either single-arm observational studies or retrospective cohort studies, the strength of evidence was rated C.

Balance between benefits and harms

In active surveillance for intermediate-risk prostate cancer, while the beneficial outcome of "reduction in medical expenses" (O1) could not be evaluated, the "reduction in the side effects from radical treatment" (O2) was considered to have a favorable effect on patients. On the other hand, outcomes of harm such as "loss of opportunity for cure" (O3) and "increase in prostate cancer mortality rate" (O4) are not favorable for patients. The benefits are higher, but the strength of evidence was equal for both benefit and harm. The majority of patients would find more benefits in active surveillance for intermediate-risk prostate cancer. However, in order to increase beneficial outcomes and reduce negative outcomes, there is a need for stricter eligibility criteria. In this CQ, a weak recommendation for active surveillance in cases of intermediate-risk prostate cancer was given by limiting it to cases that meet all the following conditions: GS3 + 4 or less, positive core number of 2 or less, PSA 10 ng/mL or less, PSAD less than 0.2 ng/mL/mL, and does not include cribriform or intraductal carcinoma.

Values, preferences, and burden of patients

As a treatment option that considers curative treatment in the future, the main focus of active surveillance is to maintain quality of life (QOL) by avoiding overdiagnosis and overtreatment. Active surveillance can be a viable treatment option for patients with intermediate-risk prostate cancer who wish to avoid physical invasion and treatment complications or for those who are unable to decide on immediate radical treatment. If the target can be limited to "intermediate-risk prostate cancer with good prognosis," and the risks of metastasis and cancer death can be reduced, active surveillance is considered to be a permissible treatment option for patients with intermediate-risk prostate cancer.

Cost and resource use

In the short term, it is considered more cost-effective than surgery or radiation therapy and is believed to reduce medical expenses. However, in the case of long-term follow-up, it cannot be denied that there is a possibility of accumulating cost burdens due to the need for multiple biopsies.

Recommendations development

It was determined that safe implementation is possible by clarifying the clinical pathological criteria for intermediate-risk patients eligible for active surveillance. Since the overall assessment of the strength of evidence was C, 89% of the guideline development group voted to "Weakly recommend."

CQ6: Is extended lymph node dissection recommended in radical prostatectomy (RP)?

Recommendation: Lymph node dissection is not necessary for low-risk cases but extended lymph node dissection is weakly recommended for intermediate- and high-risk cases.

[Level of Recommendation: Weak recommendation; Strength of Evidence: C (Weak)] (Tables 11 and 12).

Background

There are some cases where a radical prostatectomy (RP) does not result in a complete cure. The presence of lymph node metastasis is a significant factor in predicting postoperative recurrence and an important indicator in selecting adjuvant therapy. Both the NCCN and EAU guidelines recommend extended lymph node dissection for localized prostate cancer.[54,55] However, at this point, there is still no clear evidence of whether it helps to delay biochemical recurrence or extend overall survival. Furthermore, the selection criteria for patients who should undergo lymph node dissection vary among the various guidelines, and there are no unified eligibility criteria in Japan.[56–62] In light of this, we examined whether extended lymph node dissection in RP contributes to the accurate diagnostic potential of lymph node metastasis, improvement of postoperative recurrence, overall survival rate, and other outcomes.

Literature search

Through a comprehensive literature search, 333 papers were extracted. After adding five papers by hand search, 338 papers were screened. In the end, 26 papers were adopted.

TABLE 11 Committee vote results of CQ6.

	Strongly recommended	Weakly recommended	Weakly recommended not to do	Strongly recommended not to do
1st vote	0 (0%)	14 (73.7%)	5 (26.3%)	0 (0%)
2nd vote	0 (0%)	12 (63.2%)	7 (36.8%)	0 (0%)
3rd vote	0 (0%)	15 (83.3%)	3 (16.7%)	0 (0%)

TABLE 12 Components of the CQ6: P (Patients): Patients undergoing RP; I (Interventions): Extended lymph node dissection; C (Comparisons, Controls): Limited lymph node dissection/No lymph node dissection; O (Outcomes): (see below).

	Outcome	Benefit/harm	Importance (points)	Effect of intervention on outcome	Strength of evidence
O1	Improved accuracy in diagnosis of lymph node metastasis	Benefit	8	Large effect	B (Moderate)
O2	Decreased biochemical recurrence rate	Benefit	8	Small effect	C (Weak)
O3	Extension in overall survival	Benefit	9	Small effect	C (Weak)
O4	Extension of cancer-specific survival	Benefit	8	Small effect	C (Weak)
O5	Extension of metastasis-free survival	Benefit	6	Small effect	C (Weak)
O6	Increased intraoperative blood loss	Harm	6	Small effect	C (Weak)
O7	Extension of surgery time	Harm	6	Small effect	A (Strong)
O8	Onset of complications (adverse events)	Harm	7	Small effect	B (Moderate)

There were one randomized controlled trial (RCT), 5 systematic reviews, and 20 observational studies. Many reports did not have a defined lymph node dissection range, and the targets for dissection varied, but there were five papers where extended lymph node dissection and limited lymph node dissection were compared. A qualitative systematic review was conducted targeting these.

SR results

O1: Improved accuracy in diagnosis of lymph node metastasis: Regarding the improvement of lymph node metastasis diagnosis, when extended lymph node dissection is compared with limited lymph node dissection, there are some reports that the number of lymph nodes dissected increases with extended lymph node dissection, and the percentage of positive lymph nodes also increases.[63–65] Similar results have been shown in the RCT by Lestingi et al.[66] Additionally, in the systematic reviews, an increase in the number of lymph nodes dissected due to extended lymph node dissection and an improvement in the detection rate for positive lymph node metastasis have been shown, suggesting that the diagnosis of lymph node metastasis is likely to improve with extended lymph node dissection.[67–69] Based on the above, the intervention was judged to have a "Large effect" on O1, and strength of evidence was rated as B.

O2: Decreased biochemical recurrence rate: Of the 12 articles reviewed, 3 retrospective studies[63,64,70] and 1 subgroup analysis result from an RCT[66] acknowledged a decrease in biochemical recurrence due to extended lymph node dissection, comparing limited lymph node dissection and extended lymph node dissection. However, three articles that included a review comparing extended lymph node dissection and the absence of lymph node dissection did not recognize any significant difference.[71–73] Furthermore, the conclusions of the two systematic review articles[74,75] are inconsistent. On the other hand, it has been reported multiple times that even in cases with positive lymph node metastasis, the biochemical recurrence rate is low if the number of positive lymph nodes is small. It can be considered one of the therapeutic effects of lymph node dissection.[76,77] Considering the lack of RCTs, the inconsistency of subjects for lymph node dissection, and the undefined scope of dissection, the intervention was judged to have a "Small effect" on O2, with strength of evidence of C.

O3: Extension of overall survival: Few intervention studies or observational studies comparing limited and extended lymph node dissection are available, with a low risk of bias and high reliability. Systematic reviews suggest no evidence of extended overall survival due to lymph node dissection.[75] However, a recent study has reported from the SEER database that dissection of a greater number of lymph nodes may lead to an extension of overall survival in certain high-risk cases.[78] In light of this, the intervention was judged to have "Small effect" on O3, and strength of evidence is rated as C.

O4: Extension of cancer-specific survival: Few reliable intervention or observational studies have a low risk of bias comparing limited and extended lymph node dissection. Systematic reviews indicate no evident extension effect during the cancer-specific survival period due to lymph node dissection.[75] However, occasional reports suggest that the longer the cancer-specific survival period, the more lymph node dissections are performed.[72,79] Furthermore, by performing appropriate postoperative adjuvant therapy based on the information obtained from the lymph node dissection, even if there is positive lymph node metastasis, the cancer-specific survival rate can still be relatively favorable.[80,81] Considering these factors, the intervention was judged to have a "Small effect" on O4, and strength of evidence is rated C.

O5: Extension of metastasis-free survival: There are few intervention studies and observational studies that are low in bias risk and high in reliability comparing limited lymph node dissection and extended lymph node dissection. One report compared extended lymph node dissection with limited lymph node dissection and stated that 10-year metastasis-free survival was significantly better in the extended group (62.2%) than in the limited group (22.2%) ($p = 0.035$).[70] Another report stated that no significant difference was observed between the two groups in terms of a 10-year metastasis-free survival period when comparing extended lymph node dissection and no dissection in cases of

intermediate-risk prostate cancer or higher.[82] Currently, it is impossible to judge the superiority or inferiority of the prolongation effect on metastasis-free survival by extended lymph node dissection. The intervention was considered to have a "Small effect" on O5, and strength of evidence was rated as C.

O6: Increased intraoperative blood loss: Two systematic review articles[68,75] and one domestic article[65] examined intraoperative blood loss. The results of the two systematic articles do not provide a unified view of the relationship between extended lymph node dissection and intraoperative blood loss. Since both were retrospective studies, the intervention was judged to have a "Small effect" on O6, and strength of evidence was rated as C.

O7: Extension of surgery time: Four papers[65,68,75,83] were examined regarding the extension of surgery time. Although all of them are retrospective studies, it has been reported that surgery time is inevitably extended due to the need to clear more lymph nodes. Therefore, the intervention was judged to have a "Small effect" on O7, and strength of evidence was rated as A.

O8: Onset of complications (adverse events): In the six papers[65,68,69,71,75,83] examined, different conclusions were reached regarding the association between extended lymph node dissection and increased complications. A systematic review reported that no serious complications were observed with extended lymph node dissection.[68] Although there is a slight tendency for an increase in minor complications to occur, such as lymphocele and lymphedema, all of them are retrospective studies. It was judged to have a "Small effect" on O8, and strength of evidence was rated as B.

Balance between benefits and harms

In radical prostatectomy (RP), the benefits of extended lymph node dissection include "improved accuracy for diagnosis of lymph node metastasis" (O1), "decrease in biochemical recurrence rate" (O2), "extension in overall survival" (O3), "extension in cancer-specific survival" (O4), and "extension in metastasis-free survival" (O5). These are considered desirable outcomes for patients. On the other hand, the harms include an "increase in intraoperative blood loss" (O6), "extension of surgical time" (O7), and the "onset of complications (adverse events)" (O8). These are not desirable outcomes for patients. However, the benefits (desirable effects for the patient) outweigh the harms, and reports of serious patient complications are extremely rare. This led to the recommendation of extended lymph node dissection in RP.

Values, preferences, and burden of patients

In the context of radical prostatectomy, extended lymph node dissection can be considered thoroughly acceptable to the patient (and their family), given sufficient informed consent. However, if the patient (or their family) does not wish for this procedure, it is also acceptable to opt not to perform it. As of now, there is not enough evidence regarding the extension effects on the prognosis associated with extended lymph node dissection, but the pathological information on lymph node metastasis obtained by performing the lymph node dissection could be a consideration for additional postoperative treatment options (such as hormone therapy). It, therefore, could be accepted as a certain benefit.

Cost and resource use

In radical prostatectomy for prostate cancer conducted in Japan, even if extended lymph node dissection is performed, currently, there is no additional burden of medical costs.

Recommendations development

The strength of evidence for only O1 was B regarding beneficial outcomes, while the certainty for other outcomes related to therapeutic significance was C. Furthermore, some members suggested not recommending it due to the strength of evidence for harms such as O7 and O8 being A and B. However, there are few reports of serious complications following extended lymph node dissection, and the predominance of complications that do increase are minor; considering that pathological lymph node metastasis diagnosis results can serve as a criterion for selecting postoperative additional treatment options for patients, the final decision was to "weakly recommend," which was reached based on the third committee vote.

CQ7: Which is recommended as the primary treatment for locally advanced or high-risk prostate cancer: Surgical treatment or radiation therapy with hormone therapy?

Recommendation: As the primary treatment for locally advanced or high-risk prostate cancer, the superiority or inferiority of surgical treatment or radiation therapy with hormone therapy is unclear. Along with disease condition, it should be chosen considering the patient's condition, circumstances, and desires.

[Level of Recommendation: None; Strength of Evidence: C (Weak)] (Tables 13 and 14).

TABLE 13 Committee vote results of CG7.

	Strongly recommended	Weakly recommended	Weakly recommended not to do	Strongly recommended not to do	No recommendation
1st vote	0 (0%)	3 (15%)	2 (10%)	0 (0%)	15 (75%)
2nd vote	0 (0%)	2 (10%)	1 (5%)	0 (0%)	17 (85%)

TABLE 14 Components of the CQ7: P (Patients): Locally advanced or high-risk prostate cancer; I (Interventions): Surgical treatment (including preoperative hormone/chemotherapy); C (Comparisons, Controls): Hormone therapy combined with radiation therapy; O (Outcomes): (see below).

	Outcome	Benefit/harm	Importance (points)	Effect of intervention on outcome	Strength of evidence
O1	Improved overall survival rate	Benefit	9	No effect	C (Weak)
O2	Improved cancer-specific survival rate	Benefit	7	No effect	C (Weak)
O3	Improved disease-free survival rate	Benefit	7	No effect	C (Weak)
O4	Decreased biochemical recurrence rate	Benefit	5	Small inverse effect	C (Weak)
O5	Improved non-metastatic survival rate	Benefit	7	No effect	C (Weak)
O6	Increased adverse events	Harm	6	No effect	D (Very weak)
O7	Decreased QOL	Harm	6	No effect	D (Very weak)
O8	Increased medical expenses	Harm	4	Not assessable	Not assessable

Background

While radical cures can be expected for locally advanced or high-risk prostate cancer, these conditions carry a high risk of recurrence. This study examined whether surgical treatment for locally advanced or high-risk prostate cancer can be recommended compared with radiation therapy with hormone therapy.

Literature search

A comprehensive literature search yielded 331 documents from PubMed, 43 from Ichushi-Web, and 6 from a hand search, making up 380 papers. After the first screening, 301 documents were excluded, leaving 79 for examination in the secondary screening. As a result of the second screening, 23 papers were finally selected. None of the research papers were RCTs, and only seven papers had comparisons made using propensity score analysis.[84–90]

SR results

O1: Improved overall survival rate: Comparison results for the overall survival rate were found in 16 studies. Among them, eight papers (50.0%) considered both treatments to be equivalent, seven papers (43.8%) favored surgical treatment, and one paper (6.3%) favored radiation therapy (Table 15). Since the 16 papers reviewed produced different results, it was impossible to determine the superiority or inferiority of surgical treatment or radiation therapy, and the intervention was judged to have "No effect." The strength of evidence was rated as C (weak) because all of the papers were retrospective studies.

O2: Improved cancer-specific survival rate: Comparison results for cancer-specific survival rates were found in 15 studies. All of them were retrospective studies. Of these, 11 papers (73.3%)[85,88,91–99] indicated that both treatment methods were equivalent. Four papers (26.7%) suggested that surgical treatment was advantageous, while none indicated that radiotherapy was the better option (Table 1). Because the 15 papers examined produced inconsistent results, it was concluded that it is impossible to determine the superiority or inferiority of surgical treatment versus radiotherapy. Therefore, the intervention was judged to have "No effect." Furthermore, as all were retrospective studies, the strength of evidence was rated as C (weak).

O3: Improved disease-free survival rate: The improvement in combination of biochemical recurrence (BCR) and/or metastasis-free survival was evaluated in 18 studies. All were retrospective evaluations, of which 5 papers (27.8%) suggested that both treatments were equivalent, 1 paper (5.6%) indicated that surgical treatment was more beneficial, and 12 papers (66.7%) proposed that radiation therapy was more beneficial. Of these, three papers (16.7%) stated that while radiation therapy was superior in terms of BCR, there was no significant difference between the two treatments regarding the critical metastasis-free survival period (Table 1), which is important for prognosis. With these 18 papers producing differing results, we could not determine the superiority or inferiority of surgical treatment or radiation therapy, and they were judged to have "No effect." The strength of evidence was rated as C (weak) due to all the retrospective studies.

TABLE 15 Summary of outcomes in CQ7.

	Favor of surgery		Equivalent		Favor of radiation		
	Number of papers	%	Number of papers	%	Number of papers	%	Total number of papers
Overall survival rate	7	43.8	8	50.0	1	6.3	16
Cancer-specific survival rate	4	26.7	11	73.3	0	0.0	15
Disease-free survival rate	1	5.6	5	27.8	12	66.7	18
Biochemical recurrence rate	0	0.0	2	16.7	10	83.3	12
Non-metastatic survival rate	1	10.0	7	70.0	2	20.0	10

O4: Decreased BCR rate: There were 12 studies in which the results of the BCR comparison were noted. All were retrospective studies, of which 2 papers (16.7%) deemed both treatments to be equivalent, 0 papers favored surgical treatment, and 10 papers (83.3%) favored radiation therapy (Table 1). Overall, more research papers suggested that radiation therapy was favorable to BCR. In the majority (10 papers) of the 12 papers reviewed, radiation therapy was deemed favorable and judged to have a "Small inverse effect." The strength of evidence was rated as C (weak) because all of the studies were retrospective.

O5: Improved non-metastatic survival rate: Ten studies have documented the comparison results of non-metastatic survival periods. All were retrospective studies, with seven articles (70.0%)[85,86,92,94,95,97,100] claiming both treatments as equivalent, one article (10.0%) favoring surgical treatment, and two articles (20.0%) favoring radiation therapy (Table 1). Regarding non-metastatic survival rates, study papers claiming both treatments as equivalent were the most common. Judgment regarding the superiority or inferiority of surgical treatment of radiation therapy could not be made as the 10 articles reviewed produced varying results. Therefore, they were judged to have "No effect." The strength of evidence was rated C (weak) because all studies were retrospective.

O6: Increased adverse events: Only three papers documented a comparison of adverse events. All were retrospective studies, and only one study contained a statistical analysis. The only paper with statistical analysis was the retrospective study; hence, it was impossible to determine the superiority or inferiority of either surgical therapy or radiotherapy, and they were judged to have "no effect." Due to the amount and quality of the information, the strength of evidence was rated as D (very weak).

O7: Decreased quality of life (QOL): Only one document recorded a comparison of QOL. The one study reviewed concluded that QOL was equivalent, so they were judged to have "No effect." The strength of evidence was rated as D (very weak) as it was based on only one retrospective study.

O8: Increased medical expenses: None of the papers screened for this review compared healthcare costs. Therefore, an evaluation was not possible.

Balance between benefits and harms

The strength of evidence for the beneficial outcomes of "improved overall survival rate" (O1), "improved cancer-specific survival rate" (O2), "improved disease-free survival rate" (O3), "decreased BCR rate" (O4), and "improved disease-free survival rate" (O5) were all rated as C (weak). We investigated the Harms, namely "increased adverse events" (O6), "deterioration in QOL" (O7), and "increased medical expenses" (O8), but the strength of evidence was rated as D (very weak). For the impact on the outcomes, except for a "Small inverse effect" observed for "decreased BCR rate" (O4), all others received "No effect." Also, both desirable and undesirable effects for patients were almost at equivalent levels, and due to the low strength of evidence, no recommendation was given. As reflected in the recommendation statement, it is advisable to consider the patient's condition, circumstances, and preferences when making decisions.

Values, preferences, and burden of patients

The evidence supporting the recommendations is weak for all analyzed outcomes. The net benefits are expected to vary greatly depending on the patient's condition. Therefore, no clear superiority or inferiority can be stated, and decisions should be made in light of the patient's condition, circumstances, and wishes.

Cost and resource use

All treatments applied in these recommendations are covered by insurance. However, it is extremely difficult to assess and compare resources at present, including treatment progress, risk of recurrence, options for additional treatment, and their rates, effects, and duration. No research papers attempted a similar evaluation.

Recommendations development

For crucial outcomes such as "O1: Improved overall survival rate (benefit)," "O2: Improved cancer-specific survival rate (benefit)," "O3: Extension of disease-free survival rate (benefit)," and "O5: Extension of metastasis-free survival rate (benefit)," all turned out to have "No effect" and the strength of evidence for all was rated as C (weak). In terms of patient/public values, these differ significantly among individuals, and it was also difficult to compare cost and resource use. Therefore, we proposed a statement: "The superiority or inferiority of surgical or radiation therapy with hormone therapy is unclear. Along with disease condition, it should be chosen considering the patient's condition, circumstances, and desires." It was adopted as 85% of the votes were in favor in the second poll.

CQ8: Is concurrent hormone therapy recommended in high-dose radiation therapy for intermediate- to high-risk prostate cancer?

Recommendation: For intermediate-risk cases, 4–6 months of concurrently administered neoadjuvant hormone therapy is weakly recommended. For high-risk cases, a total administration period of 7–24 months, including both neoadjuvant and adjuvant hormone therapy, is weakly recommended as a concurrent treatment.

[Level of Recommendation: Weak recommendation; Strength of Evidence: C (Weak)] (Tables 16 and 17).

TABLE 16 Committee vote results of CQ8.

Strongly recommended	Weakly recommended	Weakly recommended not to do	Strongly recommended not to do
3 (15.8%)	15 (78.9%)	1 (5.3%)	0 (0%)

TABLE 17 Components of the CQ8: P (Patients): Intermediate- to high-risk prostate cancer patients; I (Interventions): High-dose radiation therapy (external radiation and brachytherapy) with hormone therapy; C (Comparisons, Controls): High-dose radiation monotherapy (external radiation and brachytherapy); O (Outcomes): (see below).

	Outcome	Benefit/harm	Importance (points)	Effect of intervention on outcome	Strength of evidence
O1	Extension of overall survival	Benefit	9	Small effect	C (Weak)
O2	Extension of biochemical recurrence-free survival	Benefit	8	Small effect	B (Moderate)
O3	Adverse events due to hormone therapy	Harm	7	Small effect	B (Moderate)
O4	Decreased QOL	Harm	7	Large effect	B (Moderate)
O5	Increased late-stage adverse events	Harm	8	No effect	B (Moderate)

Background

In radiation therapy for prostate cancer, the effectiveness of both dose escalation and combination with hormone therapy has been demonstrated, leading to the practice of high-dose radiation therapy with hormone therapy in cases of intermediate risk and higher. The usefulness of combining hormone therapy was recognized in comparative trials with a standard dose of up to 70 Gy, which prompted investigations into the effectiveness and optimal duration of combination therapy during high-dose radiation therapy exceeding 70 Gy.

Literature search

A comprehensive literature search yielded 498 papers. As a result of the screening, 41 papers were ultimately selected. The breakdown of the 41 papers showed that 5 were RCTs and the remaining 36 were retrospective cohort studies. Among the five papers on RCTs,[101–105] two were reports from the same trial.[101,102]

SR results

O1: Extension of overall survival: No contribution to overall survival was observed in one of the two RCTs that examined the additional effect of a 5-month bicalutamide monotherapy on intermediate- and high-risk groups.[105] However, in a study comparing the group that combined 2 months of goserelin with radiation therapy after 2 months of neoadjuvant combined androgen blockade (CAB) (total of 4 months) and the group that further combined 2 more years of goserelin therapy (total 28 months) after radiation,[102] the long-term combination group was significantly better ($p = 0.009$). This difference was significant only in the high-risk group ($p = 0.015$). In multiple retrospective studies, no contribution of hormone therapy was observed for intermediate risk regardless of the combination period, while on the other hand, in high-risk cases, the tendency was to recognize the effectiveness of hormone therapy as the combination period increased.[106–109] However, reports indicated that the combination of hormone therapy for more than 2 years did not contribute to overall survival.[110,111] Therefore, this was judged to have only a "Small effect" on O1, and strength of evidence was rated as C.

O2: Extension of biochemical recurrence-free survival: There were studies where the neoadjuvant hormone therapy combination of about 4–6 months had a significant effect for the intermediate-risk group[112,113] but no studies were found where the results were poor in the combination group. In terms of combination period, in three studies including an RCT,[102,106,113] the combination effect beyond 4–6 months was not shown. However, a combination of 1–3 months had poorer results than a 4- to 12-month combination.[112] A study analyzing 520 cases in Japan found better results in the hormone therapy combination group. Still, there was no difference in results between hormone therapy lasting more than 6 months and hormone therapy lasting 6 months or less.[114]

In the high-risk group, it was suggested that the combined effects of hormone therapy varied depending on the duration of the combination period. When the cutoff for the combination period was 4–6 months, two of the three studies (67%) showed a good long-term effect. Similarly, when the cutoff was 1 year, four of five studies (80%), and when it was 2 years, two of four studies (50%) showed a good long-term effect. A Japanese RCT[104] showed no difference between the 14-month and 60-month groups. On the other hand, in a foreign RCT,[102] a long-term combination was suggested to be effective ($p = 0.054$) when comparing 4 months and 28 months. In Japan, another study showed that the difference in outcome became unclear when the cutoff was 21 months for patients with one high-risk factor.[114] As a result, it is judged to have a "Small effect" on O2, and strength of evidence was rated as B.

O3: Adverse events due to hormone therapy: In an RCT comparing hormone therapy combined for 4 months and 28 months, the 5-year cumulative incidence rate of cardiovascular disorders was 7.2% in the 4-month group and 17.6% in the 28-month group ($p = 0.014$) and was higher in the long-term combination group. However, there was no difference in mortality events.[101] Similarly, there was no difference in mortality events in the cohort study.[115] Potential risks related to hormone therapy, such as the risk of fractures in the lumbar spine or forearm[116] and the risk of increasing gynecomastia,[105] were suggested. Therefore, it was judged to have a "Small effect" on O3, and strength of evidence was rated as B.

O4: Decreased QOL: Regarding urinary disorders, in an RCT that verified the combined effect of bicalutamide monotherapy for 5 months in intermediate- and high-risk cases,

there was no observed deterioration in QOL.[105] In another prospective study, relatively short-term hormone therapy of 4–8 months also had no impact,[117] and a Japanese study also showed that neoadjuvant hormone therapy did not affect IPSS.[118] Regarding sexual function, several observational studies have reported effects, including a shortening of penile length.[119] From the above, it was judged to have a "Large effect" on O4, and strength of evidence was rated as B.

O5: Increased late-stage adverse events: In an RCT that verified the combined effect of bicalutamide monotherapy for 5 months[105] and another RCT that compared combined hormone therapy for 4 and 28 months,[101] there was no increase in adverse events for both genitourinary and gastrointestinal morbidities. The results of a large-scale retrospective study in Japan contradicted these findings but had apparent factors in the patient's background. From the above, it was judged to have "No effect" on O5, and strength of evidence was rated as B.

Balance between benefits and harms

Regarding the "extension of overall survival," the strength of evidence is weak, and several reports have suggested the intervention does not contribute to prolonging overall survival. On the other hand, for the "biochemical recurrence-free survival," the combined effect of hormone therapy was confirmed under certain conditions for both intermediate- and high-risk cases. Meanwhile, the addition of hormone therapy is less likely to affect radiation-induced genitourinary and gastrointestinal morbidities after radiation therapy, and the other outcomes, "adverse events due to hormone therapy" and "deterioration in QOL," were suggested to be potential harms in a few studies, but the importance was low. Therefore, it was decided to recommend the combination of hormone therapy. However, as the results differ depending on the tumor and duration of combination therapy, it was necessary to further consider such points in the future. The recommendation statement presents candidates for the currently recommended duration of combination therapy, and it was decided to separately note the need for a detailed examination of subjects in the section for future research.

Values, preferences, and burden of patients

The combination of hormone therapy is a treatment conventionally often combined with radiation therapy and is known to potentially lead to improved treatment outcomes in terms of biochemical recurrence-free survival, so it is expected to be readily accepted. However, as this therapy can affect sexual function, patient and family preferences can vary significantly depending on factors such as age, family structure, and social background.

Cost and resource use

Hormone therapy, in conjunction with radiation therapy for prostate cancer, is a medical treatment covered by insurance. Recently, formulations for 3 or 6 months have become available, and the cost burden for patients is not an issue from the perspective of the high-cost medical expense benefit. On the other hand, because hormone therapy after recurrence often leads to a long treatment period, extending the recurrence-free period with concurrent hormone therapy is beneficial. It is also believed that it will reduce patient burden by proposing a shorter duration of hormone therapy in combination than before, depending on the risk.

Recommendations development

The benefits outweigh the harms. It was well accepted by the general public and had no issues regarding resource usage. The combined strength of evidence was rated as C; it was proposed to "Weakly recommend," and as 15.8% and 78.9% voted to strongly and weakly recommend, respectively, it was decided to "Weakly recommend."

CQ9a: Is moderate hypofractionation radiotherapy (MHF) recommended in external beam radiation therapy (EBRT) for curative purposes in prostate cancer?

Recommendation: It is weakly recommended to carry out MHF in curative EBRT for prostate cancer.

[Level of Recommendation: Weak recommendation; Strength of Evidence: A (Strong)] (Tables 18 and 19).

Background

In curative intent, EBRT for cancer, conventional fractionation radiotherapy (CF) using around 2 Gy per session once a day has been used for many years. However, one issue with this method is that it requires an extended period of 7 to 8 weeks to deliver the 70–78 Gy necessary to control prostate cancer. In recent years, it has been clarified that the α/β ratio of prostate cancer cells is smaller than that of normal tissue contrary to traditional beliefs, theoretically making hypofractionated radiotherapy with larger fractional dose and reduced therapy duration preferable. We examined whether moderately hypofractionation radiotherapy (MHF) with single doses of 2.4 to 3.4 Gy could be recommended compared with CF.

Literature search

A comprehensive literature search yielded 544 papers. After screening, 21 papers were ultimately selected. Seven were Phase III RCTs, 2 were observational studies, 10 were meta-analyses, 1 was a review, and 1 was a model-based study.

SR results

O1: Extension of overall survival: A meta-analysis of three Phase III RCTs designed to verify the non-inferiority of MHF to CF[120] and six other meta-analysis papers of Phase

TABLE 18 Committee vote results of CQ9a.

Strongly recommended	Weakly recommended	Weakly recommended not to do	Strongly recommended not to do
12 (60%)	8 (40%)	0 (0%)	0 (0%)

TABLE 19 Components of the CQ9a: P (Patients): Localized prostate cancer patients; I (Interventions): MHF; C (Comparisons, Controls): Conventional fractionation (CF); O (Outcomes): (see below).

	Outcome	Benefit/harm	Importance (points)	Effect of intervention on outcome	Strength of evidence
O1	Extension of overall survival	Benefit	9	Equivalent	A (Strong)
O2	Extension of biochemical recurrence-free survival	Benefit	8	Equivalent	A (Strong)
O3	Increased acute adverse events	Harm	6	Small effect	A (Strong)
O4	Increased late adverse events	Harm	8	No effect	A (Strong)
O5	Improved QOL/patient outcomes	Benefit	6	No effect	B (Moderate)
O6	Economic effect	Benefit	5	Large effect	C (Weak)

III RCTs, including superiority trials, making a total of seven, found no significant difference between MHF and CF, with paper[121] demonstrated non-inferiority. Therefore, it was judged to be "equivalent" to O1. Given that the results of multiple RCTs and meta-analyses were all consistent, the strength of evidence regarding "equivalence" was rated as A (strong).

O2: Extension of biochemical recurrence-free survival: Among the eight meta-analysis papers selected that compared CF and MHF in Phase III RCTs, one paper[121] proved non-inferiority, five papers showed no significant difference, one paper showed a slight shortening of the period with MHF, and one paper showed a slight extension with MHF. Therefore, MHF was judged to be "equivalent" to CF for O2. Among the eight meta-analysis papers, six showed non-inferiority or no significant difference, and two showed a slight shortening and a slight extension with MHF, respectively. Therefore, the strength of evidence regarding "equivalence" was rated as A (strong).

O3: Increased acute adverse events: In eight meta-analysis papers comparing CF and MHF in Phase III RCTs, acute gastrointestinal toxicity (GIT) showed a significant increase in six, an increasing tendency in one, and no significant difference in another. Acute genitourinary toxicity (GUT) showed no significant difference in all eight reports. The majority of acute GIT cases were Grade 2, and severe cases were scarcely mentioned. From the above, MHF was judged to have a "Small effect" in terms of acute GI toxicity on O3. Seven of the eight meta-analysis papers showed a significant increase or an increasing tendency, while one showed no significant difference. Therefore, the strength of evidence was rated as A (strong).

O4: Increased late adverse events: In 11 meta-analysis papers comparing CF and MHF in Phase III RCTs, no significant difference in late GU toxicity was reported in nine, and a significant increase (mostly Grade 2/3) with MHF was reported in two. Late GI toxicity showed no significant difference in 10 reports and a significant reduction with MHF in 1. Therefore, MHF was judged to have "No effect." Of the 11 meta-analysis papers, 2 reports of late GU toxicity showed a significant increase (mainly Grade 2/3) with MHF and 1 report of late GI toxicity showed a significant reduction with MHF, while the rest showed no significant difference. The strength of evidence showing "No effect" was rated as A (strong).

O5: Improved QOL/patient outcomes: In six papers regarding Phase III RCTs comparing CF and MHF, one systematic review,[122] and one cohort study based on a large database, all eight reports showed no significant difference considered clinically meaningful between CF and MHF. Therefore, MHF was judged to have "No effect" on O5. There is no meta-analysis, and the strength of evidence showing "No effect" is rated as B (moderate).

O6: Economic effect: All three adopted papers reported and calculated a meaningful medical cost reduction effect from using MHF instead of CF. However, all these reports are based on calculations in the United States and Europe, and there were no reports applicable to the current situation in Japan, which was judged to have a high bias risk. Nonetheless, the reduction in medical costs is evident under Japan's insurance system, and MHF was judged to have a "Large effect" on O6. As this systematic review is based on evaluations in the West, the strength of evidence was rated as C (weak).

Balance between benefits and harms

While the important benefits of MHF, namely "extension of overall survival" (O1) and "extension of biochemical recurrence-free survival" (O2), were not observed, MHF and CF were considered as "equivalent," and the strength of evidence was rated as A (strong). Also, in terms of significant harm, MHF was judged to have "No effect" on the "increase in late adverse events" (O4), and the strength of evidence was rated as A (strong). With MHF, a significant reduction in the total treatment period is possible, which is clearly beneficial in terms of patient convenience and reduction of the burden; also reduces the burden in terms of radiotherapy. Furthermore, under the current insurance system in Japan, a medical cost reduction effect can be obtained, and this benefit is considered significant. On the other hand, with MHF, while a slight increase in acute GI disorders (most of which are Grade 2) is observed, the majority of acute disorders disappear a few months after the end of treatment. Therefore, it was judged that the benefits of convenience and burden reduction clearly outweigh the harm of a slight increase in acute GI disorders.

Values, preferences, and burden of patients

The convenience and reduction of burden for both patients and medical staff due to the short duration of treatment are apparent, and patient preference for this approach is high in actual clinical practice. In fact, multi-institutional research studies conducted in Canada and Australia on patients with localized prostate cancer undergoing radiation therapy reported that shortening the duration of radiation therapy is a factor significantly associated with higher patient preference values, along with the resulting reduction in biochemical recurrence (BCR) and adverse events, and the avoidance of invasive positional marker placement.[123]

Cost and resource use

Although no cost-effectiveness evaluation based on domestic data has been conducted, the amount borne by patients under the current health insurance remuneration settings for medical treatment in Japan is reduced.

Recommendations development

While the risks and benefits are equal and highly certain, the apparent reduction in burden for patients and clinical practice led to expectations of a high-level recommendation. However, 60% of votes at the recommendation decision meeting were for "strongly recommend" and 40% for "weakly recommend," resulting in a final decision of "weakly recommend."

CQ9b: Is ultrahypofractionation radiation recommended in curative external beam radiotherapy (EBRT) for prostate cancer?

Recommendation: It is weakly recommended to perform UHR in curative EBRT for low-risk and intermediate-risk prostate cancer.

[Level of Recommendation: Weak recommendation; Strength of Evidence: C (Weak)] (Tables 20 and 21).

TABLE 20 Committee vote results of CQ9b.

Strongly recommended	Weakly recommended	Weakly recommended not to do	Strongly recommended not to do
0 (0%)	17 (85%)	3 (15%)	0 (0%)

Background

In EBRT for curative cancer treatment, the traditional approach has been to administer a dose of about 2 Gy per day in conventional fractionation radiotherapy (CF), which has been used for many years. However, the challenge has been the lengthy period of 7–8 weeks required for the administration of the 70 to 78 Gy needed for the control of prostate cancer. In recent years, it has been clarified that the α/β ratio of prostate cancer cells is smaller than that of normal tissue, contrary to traditional beliefs, theoretically making hypofractionated radiotherapy with larger fractional doses and reduced duration of therapy preferable. We examined whether UHR, which involves 6.0–8.0 Gy per dose, can be recommended over CF.

Literature search

A comprehensive literature search extracted 544 articles. Following the screening, nine articles remained. The breakdown of these nine articles was as follows: two were Phase III RCTs, one was a meta-analysis, two were Phase II trials, one compared trend scores and matches, one was a systematic review, and the remaining two were retrospective cohort studies. Also, one of the Phase III RCTs was a report related only to acute adverse events.

SR results

O1: Extension of the overall survival period: With regard to Phase III RCTs, there was only one report targeted intermediate- to high-risk (mostly intermediate) prostate cancer, and there was no significant difference in overall survival rate between UHR and CF over 5 years.[124] Also, since there were no reports with sufficient cases and follow-up periods, the effect on O1 (extension of overall survival period, benefit/importance 9 points) was considered "Equivalent." The strength of evidence for O1 was rated as C (weak).

O2: Extension of biochemical recurrence-free survival: Non-inferiority was proven in one article on Phase III RCT,[124] and there was no significant difference in one meta-analysis article.[125] Furthermore, since good results have been reported in cohort studies also, the effect on O2 was also judged to be "Equivalent." The strength of evidence for O2 was rated as B (moderate).

O3: Increased acute adverse events: In two Phase III RCTs reporting adverse events, one trial reported a significant

TABLE 21 Components of the CQ9b: P (Patients): Localized prostate cancer patients; I (Interventions): Ultrahypofractionation radiation; C (Comparisons, Controls): Conventional fractionation (CF); O (Outcomes): (see below).

	Outcome	Benefit/harm	Importance (points)	Effect of intervention on outcome	Strength of evidence
O1	Extension of overall survival	Benefit	9	Equivalent	C (Weak)
O2	Extension of biochemical recurrence-free survival	Benefit	8	Equivalent	B (Moderate)
O3	Increased acute adverse events	Harm	6	No effect	C (Weak)
O4	Increased late adverse events	Harm	8	No effect	B (Moderate)
O5	Improved QOL/patient outcomes	Benefit	6	No effect	C (Weak)
O6	Economic effect	Benefit	5	Large effect	C (Weak)

increase in urinary tract events in UHR,[124] and the other trial reported no significant difference in gastrointestinal and urinary adverse events.[126] Meanwhile, cohort studies have also reported that the frequency of acute adverse events in UHR is not high. Different results have been reported in Phase III RCTs, and cohort studies report that the frequency of acute adverse events in UHR is not high. Therefore, it was judged as having "No effect" on O3, and the strength of evidence was rated as C (weak).

O4: Increased late adverse events: In both a Phase III RCT paper[124] and a meta-analysis paper,[125] no significant difference was observed in late adverse events. As similar results have been reported in cohort studies, it was judged to have "No effect" on O4, and the strength of evidence was rated as B (moderate).

O5: Improved QOL/patients outcomes: In a Phase III RCT paper,[124] there was no significant deterioration observed in any aspect other than the urinary tract 1 year after UHR in terms of late adverse events. Conversely, in a multicenter pooled analysis, UHR significantly relieved late adverse events in both the digestive and urinary systems compared to MHF.[127] Given these mixed reports—some indicating an improvement in patient-reported outcomes following UHR and others pointing to a temporary deterioration—UHR was judged as having "No effect" on O5, and the strength of evidence was rated as C (weak).

O6: Economic impact: Although only one paper[128] showed superiority in terms of the economic impact of UHR, the cost of this method in Japan is lower than that of CF, and there are clear financial benefits when outpatient costs, etc., are considered. Therefore, UHR was considered to have a "Large effect" on O6. As the evidence in the literature is based on evaluations in Europe and the United States, the strength of evidence was rated as C (weak).

Balance between benefits and harms

Although the strength of evidence for the beneficial outcomes O1 and O2 from using UHR are deemed to be at level C (weak) and B (moderate), respectively, the superiority of UHR is not clear and, therefore, was considered "Equivalent" to the effect of CF. On the other hand, UHR was judged to have "No effect" on O4, an outcome of significant harm, and strength of evidence was rated as B (moderate). In terms of overall treatment duration, this was significantly shortened by UHR, reducing the burden on patients and radiotherapy providers and clearly superior in terms of convenience. As a result, the overall benefit was determined to exceed the harm.

Values, preferences, and burden of patients

In recent years, the number of UHR procedures performed has been increasing. The treatment itself is less invasive for patients and the treatment period is significantly shorter, which is very important. If non-inferiority to CF and MHF can be demonstrated in ongoing clinical trials, patient demand is expected to become very high and widespread.

Cost and resource use

Cost-effectiveness based on domestic data has not been assessed. However, in the current Japanese medical treatment remuneration settings under national insurance, the amount of the patient responsible will be significantly reduced.

Recommendations development

Given the strength of evidence for the benefits and harms described in the "Balance between Benefits and Harms" is not high, there is insufficient evidence to recommend UHR strongly. Additionally, the current evidence is mainly focused on cases with low-to-intermediate risk, leading to a "Weak recommendation" of UHR for localized prostate cancer with low-to-intermediate risk.

CQ10: Is tri-modality therapy with low-dose-rate brachytherapy (LDR), external beam radiotherapy (EBRT), and hormone therapy recommended as radiation therapy for high-risk prostate cancer?

Recommendation: It is weakly recommended to carry out tri-modality therapy with LDR, EBRT, and hormone therapy as radiation therapy for high-risk prostate cancer.

[Level of Recommendation: Weak recommendation; Strength of Evidence: C (Weak)] (Tables 22 and 23).

Background

In high-risk prostate cancer, microscopic extracapsular and metastatic foci may already be present at the time of diagnosis, and treatments that can affect these microscopic foci are needed for a complete cure. LDR has traditionally been performed as a standalone treatment for low-risk localized prostate cancer. Recently, the usefulness of tri-modality therapy, combining LDR with EBRT and hormone therapy, has been shown for high-risk localized prostate cancer as well. We examined whether tri-modality therapy can be recommended over EBRT + hormone therapy.

Literature search

A comprehensive literature search yielded 532 articles. As a result of the screening, 12 articles were ultimately selected. Among the 12 articles, 3 were RCTs, 2 were meta-analyses, 1 was a prospective cohort study, and the remaining 6 were retrospective cohort studies. All three RCT papers were regarding the large-scale ASCENDE-RT trial that compared tri-modality therapy with EBRT + hormone therapy, covering oncological outcomes,[129] adverse events,[130] and QOL.[131]

TABLE 22 Committee vote results of CQ10.

Strongly recommended	Weakly recommended	Weakly recommended not to do	Strongly recommended not to do
1 (5.3%)	16 (84.2%)	2 (10.5%)	0 (0%)

TABLE 23 Components of the CQ10: P (Patients): High-risk prostate cancer patients; I (Interventions): Tri-modality therapy of LDR + EBRT + hormone therapy; C (Comparisons, Controls): EBRT + hormone therapy; O (Outcomes): (see below).

	Outcome	Benefit/harm	Importance (points)	Effect of intervention on outcome	Strength of evidence
O1	Improved biochemical recurrence-free rate	Benefit	8	Large effect	B (Moderate)
O2	Improved overall survival rate	Benefit	9	Small effect	C (Weak)
O3	Improved metastasis-free survival rate	Benefit	8	Small effect	C (Weak)
O4	Shorter treatment period	Benefit	4	Not assessable	Not assessable
O5	Reduced QOL	Harm	8	Small effect	C (Weak)
O6	Adverse events	Harm	8	Small effect	C (Weak)
O7	Development of secondary cancer	Harm	4	Not assessable	Not assessable

SR results

O1: Improved biochemical recurrence-free rate: The results of the ASCENDE-RT trial, a large-scale RCT related to this CQ, showed that the 9-year biochemical recurrence-free rate after treatment for high-risk prostate cancer was significantly better at 83% in the tri-modality group, compared with 62% in the control group, which was the EBRT + hormone therapy group.[129] A retrospective cohort study of 320 high-risk prostate cancer cases also showed significantly better median biochemical recurrence-free survival in the tri-modality group (9.8 years), compared with the EBRT + hormone therapy group (6.5 years).[132] Therefore, tri-modality therapy was judged to have a "Large effect" on O1, and strength of evidence was rated as B.

O2: Improved overall survival rate: The ASCENDE-RT trial did not show a difference in terms of overall survival rate between the tri-modality therapy group and the EBRT + hormone therapy group.[129] On the other hand, a large-scale cohort study of 25 038 unfavorable cancer patients showed that the overall survival rate, when sorted by the propensity score matching method, was significantly better in the tri-modality therapy group compared with the EBRT + hormone therapy group, with a hazard ratio of 0.74.[133] Another cohort study also showed a significantly better median overall survival in the tri-modality therapy group (12.3 years) compared with the EBRT + hormone therapy group (9.1 years) ($p < 0.001$).[132] Due to the discrepancy between RCT and cohort study results, tri-modality therapy was judged to have a "Small effect" on O2 with strength of evidence rated as C.

O3: Improved metastasis-free survival rate: The ASCENDE-RT did not show a difference in metastasis-free survival rate between the tri-modality therapy group and the EBRT + hormone therapy group.[129] On the other hand, two retrospective cohort studies on high-risk prostate cancer showed that the metastasis-free survival rate was best in the tri-modality therapy group compared with EBRT + hormone therapy and surgical treatment.[134,135] Due to the discrepancy between the RCT and cohort study results, tri-modality therapy was judged to have a "Small effect" on O3 with the strength of evidence of C.

O4: Shorter treatment period: There were no studies among the searched articles that mentioned short-term treatment period. Therefore, tri-modality therapy was judged as "Not assessable."

O5: Reduced QOL: The ASCENDE-RT trial showed that urinary, sexual, and physical function declined significantly in the tri-modality group compared with the EBRT + hormone therapy group.[131] The ASCENDE-RT is an RCT among Canadians, and there may be differences in technology and brachytherapy quality control between Canada and Japan. Therefore, tri-modality therapy was judged to have a "Small effect" on O5 with strength of evidence of C.

O6: Adverse events: The ASCENDE-RT showed that the tri-modality group had significantly more severe urinary problems compared with the EBRT + hormone therapy group.[130] In contrast, in the Japanese Prostate Cancer Outcome Study of Permanent Iodine-125 Seed Implantation (J-POPS) report from multiple facilities in Japan, the incidence of severe urinary disorders was extremely low (<1.3%) in the 3-year period after LDR + EBRT in 547 cases,[136] suggesting that there may be slight differences in technology and brachytherapy quality control between Japan and Canada. Therefore, tri-modality therapy was judged to have a "Small effect" on O6 with strength of evidence of C.

O7: Development of secondary cancer: Although there are papers on the occurrence of secondary cancers after radiation therapy for prostate cancer, there were no studies comparing the tri-modality therapy and EBRT + hormone therapy. Therefore, tri-modality therapy was judged to be "Not assessable."

Combined assessment of the strength of evidence

The important outcomes in this CQ were O1, 2, 3, 5, and 6, and all outcomes except O1 had strength of evidence of C. Therefore, the combined assessment was level C.

Balance between benefits and harms

A "Large effect" was noted in the "biochemical recurrence-free rate" (O1) with tri-modality therapy compared with EBRT + hormone therapy. Although no significant difference

was observed in the overall survival rate or metastasis-free survival rate in one large-scale RCT trial (ASCENDE-RT), multiple cohort studies confirmed its efficacy. Therefore, it was deemed to have sufficient benefits with respect to the antitumor effect. The harms, which are "reduced QOL" (O5) and "adverse events" (O6), were significantly worse with tri-modality therapy, especially in terms of urination, as compared with EBRT + hormone therapy. However, there was no evidence of severe or prolonged effects, and it was determined that the benefits outweighed the harms.

Values, preferences, and burden of patients

LDR has a history as a minimally invasive treatment for low-risk prostate cancer and has been generally accepted in Japan. The accompanying EBRT typically requires around 15 treatments, which is less than CF. Hormone therapy is often carried out for 6 to 24 months, but it is thought that adverse events are within tolerable range.

Cost and resource use

In terms of LDR, EBRT, and hormone therapy in tri-modality therapy, none of these forms of treatment for prostate cancer present a significant physical, temporal, or economic burden compared to other treatments. Treatment is provided by underinsured medical care, and the cost is judged to be equivalent to other radiation therapy or surgery.

Recommendations development

Tri-modality was considered an acceptable treatment because the balance of benefits outweighed the harms and was favorable in terms of public acceptance and resource utilization. A comprehensive assessment resulted in the strength of evidence being rated as C and led to a proposal to weakly recommend tri-modality therapy. This was finalized with more than 80% of the votes.

CQ11: For primary hormone therapy for metastatic castration-sensitive prostate cancer (mCSPC), which is recommended as a combination drug, docetaxel (DTX), or a novel androgen receptor signaling inhibitor (ARSI)?

Recommendation: It is weakly recommended to use ARSI as a combination drug for primary hormone therapy for mCSPC.

[Level of Recommendation: Weak recommendation; Strength of Evidence: B (moderate)] (Tables 24 and 25).

Background

In overseas Phase III trials, it has been reported that clinical outcomes, such as overall survival, improved when combining primary hormone therapy with either docetaxel (DTX) or ARSI for metastatic prostate cancer. However, evidence directly comparing combination drugs is limited, and the standard treatment for untreated metastatic prostate cancer has not been established. An analysis was conducted to determine whether DTX or ARSI was superior as a combination drug for primary hormone therapy for metastatic prostate cancer.

Literature search

As a result of the literature search for this CQ, 377 papers were retrieved. Two more papers were added by hand search, and a total of 379 papers were screened independently by two individuals for each paper, resulting in the exclusion of 338 papers. The remaining 41 papers were then independently screened in depth by two individuals for each paper. As a result, seven papers extracted from the literature search and two more added by hand search, bringing the total to nine, were selected and validated as the adopted papers.

SR results

O1: Extension of overall survival: Significant extension of overall survival has been achieved in some studies on abiraterone versus DTX. Network meta-analysis has shown the superiority of abiraterone over DTX, with hazard ratios reported as 0.80 (95% CI: 0.66–0.96)[137] and 0.77 (95% CI: 0.65–0.92).[138] There have been many reports suggesting the superiority of ARSI, but there has been no report showing the superiority of DTX. However, most of the results are based on indirect comparison. Consequently, we assessed it as being "Small effective" for O1 with strength of evidence of B.

O2: Extension of radiographic progression-free survival: Most reports have shown a significant extension of radiological progression-free survival with ARSI, mainly abiraterone, compared with DTX. According to network meta-analysis, the superiority of abiraterone, enzalutamide, and apalutamide over DTX was shown with respective to hazard ratios and reported as 0.71 (95% CI: 0.59–0.86), 0.61 (95% CI: 0.49–0.75), and 0.74 (95% CI: 0.57–0.95),[139] while the superiority of abiraterone and enzalutamide was shown in surface C under the cumulative ranking (SURCRA) as 42.7% and 57.3%, respectively.[140] The superiority of abiraterone over DTX was shown with hazard ratios of 1.59 (95% CI: 1.36–1.86),[141] and 0.59 (95% CI: 0.46–0.75),[137] while the superiority of abiraterone, enzalutamide, and apalutamide was shown with hazard ratios of 0.77 (95% CI: 0.65–0.91), 0.58 (95% CI: 0.44–0.77), and 0.72 (95% CI: 0.57–0.92), respectively.[138] An RCT reported the superiority of abiraterone with a hazard ratio of 0.69 (95% CI: 0.50–0.95).[142]

Table 24 Committee Vote Results of CQ11.

Strongly recommended	Weakly recommended	Weakly recommended not to do	Strongly recommended not to do	Abstention (COI)
2 (15.4%)	11 (84.6%)	0 (0%)	0 (0%)	6

Table 25 Component of the CQ11: P (Patients): mCSPC patients; I (Interventions): Primary hormone therapy combined with ARSI; C (Comparisons, Controls): Primary hormone therapy combined with DTX; O (Outcomes): (see below).

	Outcome	Benefit/harm	Importance (Points)	Effect of intervention on outcome	Strength of evidence
O1	Extension of overall survival	Benefit	9	Small effect	B (Moderate)
O2	Extension of radiographic progression-free survival	Benefit	8	Large effect	B (Moderate)
O3	Maintained QOL	Benefit	7	Large effect	B (Moderate)
O4	Increased medical expenses	Harm	5	Large effect	B (Moderate)
O5	Fatigue	Harm	6	No effect	B (Moderate)
O6	Pain relief	Benefit	6	Small effect	B (Moderate)
O7	Neurological symptoms	Harm	6	Not assessable	Not assessable
O8	Few serious adverse events (Grade 3 or above)	Benefit	8	Small effect	B (Moderate)

However, most of these results were from indirect comparisons. Therefore, it was assessed as having a "Large effect" on O2 with strength of evidence of B.

O3: Maintained QOL: The change over time in QOL after administration of abiraterone was reported to be significantly better than after DTX administration at all points (3, 6, 9, and 12 months), and the Bayesian probability at these points (3, 6, 9, and 12 months) according to network meta-analysis was 99.7%, 94.5%, 97.0%, and 92.3%.[143] However, the above results were from indirect comparisons. Consequently, it was judged to have a "Large effect" on O3 with strength of evidence of B.

O4: Increased medical costs: Multiple analyses showed the superiority of DTX over abiraterone in terms of costs, with the incremental cost-effectiveness ratio being $295 212 for abiraterone and $34 723 for DTX. However, such ratios are based on an indirect comparison based on data from the United States.[144] Consequently, it was judged to have a "Large effect" on O4 with strength of evidence of B.

O5: Fatigue: There was no significant difference in the frequency of fatigue emergence between patients administered abiraterone and DTX (the frequency of Grade 3 or above fatigue was 2% and 4%, respectively, in the abiraterone and the DTX groups).[142] The above result is based on the RCT, but the data for Grade 2 or less were unknown. Consequently, it was assessed as having "No effect" on O5 with strength of evidence of B.

O6: Pain relief: A network meta-analysis reported significant improvement in pain after abiraterone compared to DTX in a longitudinal evaluation (Bayesian probability for 3, 6, 9, and 12 months being 88.0%, 100%, 100%, and 99.9%, respectively).[143] However, the results of an RCT showed that there was no significant difference in the frequency of skeletal-related events between the two groups (26% in the abiraterone group and 30% in the DTX group).[142] However, the above results include those based on indirect comparison. Consequently, we assessed it as having a "Small effect" on O6 with strength of evidence of B".

O7: Neurological symptoms: No specific data on neurological symptoms were provided in the studies selected for review. Consequently, we assessed its effect on O7 as "not assessable."

O8: Few serious adverse events (grade 3 or above): Regarding the onset of serious adverse events associated with the administration of ARSI and DTX, results generally indicating the superiority of ARSI have been reported. According to a network meta-analysis, enzalutamide and apalutamide showed superiority with respective hazard ratios of 0.56 (95% CI: 0.35–0.92) and 0.44 (95% CI: 0.24–0.79),[139] while abiraterone, enzalutamide, and apalutamide showed superiority with respective odds ratios of 0.06 (95% CI: 0.03–0.11), 0.04 (95% CI: 0.02–0.07), and 0.04 (95% CI: 0.02–0.08).[138] However, some reports have suggested there is little difference. Most of the above results were based on indirect comparisons. Therefore, it has been judged as having a "Small effect" on O8, and the strength of evidence is rated as B.

Balance between benefits and harms

The beneficial outcomes of primary hormone therapy for mCSPC are "extension of overall survival" (O1), "extension of radiographic progression-free survival" (O2), "maintained QOL" (O3), and "fewer severe adverse events" (Grade 3 or higher) (O8), which were found superior when ARSI was co-administered. On the other hand, it was judged to be inferior when co-administrating ARSI in the outcome of harms and "increased medical expenses" (O4), although this is an evaluation based on the analysis by the US insurance system.

Values, preferences, and burden of patients

ARSI can be easily administered orally, and from a safety perspective, including a low rate of severe adverse events and the simplicity of oral administration, ARSI is thought to be preferred by patients and the public. Furthermore, considering the conferred benefits of excellent cancer control and maintained QOL, it is believed that the treatment of co-administering ARSI in primary hormone therapy for mCSPC will be widely accepted by patients and the public.

Cost and resource use

As a co-medication for primary hormone therapy against mCSPC, DTX is superior to ARSI from the standpoint of patient economic burden. Moreover, there are reports demonstrating the superior effect of DTX by analyzing the cost-

effectiveness of both drugs, but this is also based on an analysis of the US insurance system.

Determinations development

In a comprehensive evaluation of the overall outcomes, the benefits outweigh the harms, and public acceptance is good. Based especially on the superiority in critical outcomes and strength of evidence, it was proposed to "weakly recommend the use of ARSI in primary hormone therapy for mCSPC" on the basis of more than 80% of the votes.

CQ12: Is a novel androgen receptor signaling inhibitor (ARSI) recommended as primary therapy for non-metastatic castration-resistant prostate cancer (nmCRPC)?

Recommendation: ARSI is weakly recommended as a primary treatment for high-risk nmCRPC at high risk of progression.

[Level of Recommendation: Weak recommendation; Strength of Evidence: B (moderate)] (Tables 26 and 27).

Background

nmCRPC is defined as a condition where, despite the administration of ADT, an increase in PSA levels has been observed, yet no distant metastasis was detected in conventional imaging examinations such as CT, bone scintigraphy, and MRI. There has been no standard criterion for the timing of imaging diagnosis or the selection of therapeutic drugs for such conditions. Since 2018, evidence has emerged that the use of ARSI in high-risk nmCRPC cases prolongs the time to metastatic progression by approximately 2 years longer than in the placebo group. Also, since nmCRPC cases are asymptomatic, maintaining QOL in long-term treatment is important. We examined whether an early diagnosis of nmCRPC and the early introduction of ARSI are necessary.

Literature search

We primarily focused on articles regarding international randomized placebo-controlled trials using apalutamide, enzalutamide, or darolutamide as the primary treatment for nmCRPC. To prove the outcomes related to the CQ, 132 papers were extracted in the primary screening. Ultimately, 30 papers were selected in the secondary screening, and they were used to review the outcomes related to the CQ. These included 12 RCTs, 4 observational studies, 9 meta-analyses, and 5 reviews.

SR results

O1: Suppression of metastasis: Three international placebo-controlled randomized trials (SPARTAN study, PROSPER study, and ARAMIS study) investigated the performance of apalutamide, enzalutamide, and darolutamide in nmCRPC where the PSA doubling time was less than 10 months using metastasis-free survival as the primary evaluation item.[145–147] As a result, there was a significant prolongation of metastasis-free survival in the ARSI group of the above three drugs compared to the placebo group (hazard ratio in each study: 0.28 (95% CI: 0.23–0.35),[145] 0.29 (95% CI: 0.24–0.35),[146] and 0.41 (95% CI: 0.34–0.50)[147]). The three ARSIs consistently demonstrated prolonged metastasis-free survival, with O1 rating a "Large effect" and the strength of evidence of A (strong).

O2: Extension of overall survival: In the SPARTAN study, PROSPER study, and ARAMIS study, apalutamide, enzalutamide, and darolutamide significantly prolonged overall survival compared with the placebo (hazard ratio in each study: 0.78 (95% CI: 0.64–0.96),[148] 0.69 (95% CI: 0.53–0.88),[149] and 0.73 (95% CI: 0.61–0.89)[150]). All three ARSIs were consistently shown to extend overall survival and were rated as having a "Large effect" on O2, with strength of evidence of A (strong).

TABLE 26 Committee Vote Results of CQ12.

Strongly recommended	Weakly recommended	Weakly recommended not to do	Strongly recommended not to do	Abstention (For COI)
10 (62.5%)	6 (37.5%)	0 (0%)	0 (0%)	4

TABLE 27 Components of the CQ12: P (Patients): nmCRPC patients; I (Interventions): ARSI + Androgen deprivation therapy (ADT); C (Comparisons, Controls): ADT/Combined androgen blockade (CAB) therapy; O (Outcomes): (see below).

	Outcome	Benefit/harm	Importance (points)	Effect of intervention on outcome	Strength of evidence
O1	Suppression of metastases	Benefit	8	Large effect	A (Strong)
O2	Extension of overall survival	Benefit	9	Large effect	A (Strong)
O3	Maintained QOL	Benefit	6	Small effect	B (Moderate)
O4	Reduced PSA level	Benefit	4	Large effect	A (Strong)
O5	Extension of time to chemotherapy	Benefit	5	Large effect	A (Strong)
O6	Suppression of skeletal-related events	Benefit	5	No effect	C (Weak)
O7	Increased medical expenses	Harm	5	No effect	D (Very Weak)
O8	Adverse events	Harm	6	Small effect	B (Moderate)

O3: Maintained QOL: As an additional analysis of the three international placebo-controlled randomized trials, the results of examining health-related quality of life (HRQOL) have been reported.[151–153] All evaluations used HRQOL scales, such as FACT-P and EORTC QLQ-PR25. Although no significant superiority was shown after any ARSI treatments, QOL was maintained. As there are systematic reviews showing similar results, ARSI was judged to have a "Small effect" on O3, and the strength of evidence was rated as B (moderate).

O4: Decrease in PSA levels: In the SPARTAN study, a decrease in PSA levels 12 weeks after randomization was obtained in 89.7% of the apalutamide group versus 2.2% in the placebo group.[146] In the PROSPER study, a decrease in PSA values of more than 50% was achieved in 76% of the enzalutamide group versus 2% in the placebo group.[146] In the ARAMIS study, the darolutamide group had a PSA progression-free survival period of 33.2 months compared with 7.3 months in the placebo group (hazard ratio: 0.13 (95% CI: 0.11–0.16), $p < 0.001$).[147] All three ARSI drugs showed strong effects in reducing PSA levels. From consistent significant reductions in PSA levels in reliable RCTs and retrospective studies, ARSIs were judged to have a "Large effect" on O4, and the strength of evidence was rated as A (strong).

O5: Extension of time to chemotherapy: In the final analysis of the SPARTAN study, compared with the placebo group, the hazard ratio was 0.63 (95% CI: 0.49–0.81, $p = 0.0002$), and the median value was not achieved in either group.[148] In the final analysis of the PROSPER study, compared with the placebo group, the hazard ratio was 0.54 (95% CI: 0.44–0.67, no statistical significance test), and the median value was not achieved in either group.[150] In the final analysis of the ARAMIS study, compared to the placebo group, the hazard ratio was 0.58 (95% CI: 0.44–0.76, $p < 0.001$), and at 3 years, 83% of patients in the darolutamide group versus 75% in the placebo group had not received chemotherapy, with the median value not achieved in either group.[149] All literature acknowledged the effect of ARSIs in extending the period until chemotherapy in high-risk nmCRPC compared to placebo. Therefore, ARSIs were judged to have a "Large effect" on O5, and the strength of evidence was rated as A (strong).

O6: Suppression of skeletal-related events: The final analysis of the ARAMIS study yielded a hazard ratio of 0.48 (95% CI: 0.29–0.82, $p = 0.005$). The median was not achieved in either group.[149] According to the meta-analysis of the SPARTAN, PROSPER, and ARAMIS studies, there is a report of a 2.242 times higher risk of bone fractures in the ARSI group compared with the placebo group.[154] Based on these results, ARSIs were judged to have "No effect" on O6 (suppression of skeletal-related events, benefit/importance score 5), and the strength of evidence is rated as C (weak).

O7: Increase in medical expenses: It was reported that using enzalutamide for nmCRPC could extend the time to mCRPC, thereby reducing the medical costs associated with mCRPC treatment. When estimating the insurance premium amount for 3 years, it was suggested that the planned treatment costs would be offset.[155] This estimation is based on foreign research data, and no calculation of medical costs from observational studies in Japan has been conducted. Hence, ARSI was judged to have "No effect" on O7, and the strength of evidence was rated as D (very weak).

O8: Adverse events: In comparing the enzalutamide group and the placebo group, fatigue was reported at 46% and 22%, and musculoskeletal events at 34% and 23%, respectively.[150] In an RCT involving darolutamide, the drug discontinuation rate due to adverse events was 8.9% in the darolutamide group and 8.7% in the placebo group, showing almost no difference between the groups.[147] For apalutamide, the frequency of adverse events, such as rashes, falls, and fractures, was higher than in the placebo group. Among the Japanese population, the incidence of rash is high, with a 55.88% rash occurrence rate reported in the subgroup analysis of Japanese participants in the SPARTAN study.[156] Based on the results of RCTs and meta-analyses, there are differences in the types and frequencies of each adverse event. Therefore, ARSI is judged to have a "Small effect" on O8, and the strength of evidence was rated as B (moderate).

Balance between benefits and harms

The beneficial outcomes of ARSIs include "suppression of metastasis" (O1), "extension of overall survival" (O2), "maintained QOL" (O3), "decrease in PSA value" (O4), "extension of time to chemotherapy" (O5), and "suppression of skeletal related events" (O6), all of which are considered favorable for patients. On the other hand, the harms, which are "increases in medical expenses" (O7) and "adverse events" (O8), are not desirable for patients. However, the beneficial outcomes outweigh the harms, and the strength of evidence is higher. Consequently, ARSI is recommended for nmCRPC.

Values, preferences, and burden of patients

Changes in QOL and the occurrence of adverse events due to long-term administration of ARSI can impact the continuation of treatment, physically and mentally. Stabilizing low PSA levels and controlling metastatic recurrence with ARSI can provide mental reassurance. However, occurrences like falls, fractures, and high blood pressure can have a harmful impact on daily life.

Cost and resource use

While ARSI drugs are expensive, a report from the United States indicates that postponing the onset of metastasis with ARSI can offset the costs compared with cases where metastasis occurs early. However, the impact on medical expenses in Japan is unclear.

Recommendations development

Based on the results of three global prospective trials, six beneficial outcomes had strong evidence. On the other hand,

there was weak evidence for two harms, which cannot be ignored when considering long-term ARSI treatment. Including the fact that nearly 40% of votes were for "weakly recommend," the decision was made to weakly recommend ARSI as a primary treatment for nmCRPC.

CQ13: Following upfront therapy (novel ARSI/docetaxel (DTX)) for mCSPC, which is recommended as the primary treatment for mCRPC, unused ARSI, or DTX?

Recommendation: There is no clear evidence of superiority between unused ARSI and DTX as the first-line treatment for mCRPC after upfront therapy (ARSI/DTX) for mCSPC. It is desirable that the choice be made according to the patient's condition and wishes. (This CQ was chosen as a future research question because not enough evidence could be collected under current conditions).

[Level of Recommendation: No Recommendation; Strength of Evidence: Not assessable] (Tables 28 and 29).

Background

The primary treatment for mCSPC has undergone significant changes in recent years. There is ample evidence that combining ADT with ARSI or DTX as initial treatment, instead of traditional ADT monotherapy or CAB therapy, can extend overall survival. However, it is a new and important clinical issue in which drugs are recommended to use for treatment in mCRPC that has progressed after this upfront therapy for mCSPC. Therefore, we decided to pose this CQ.

Literature search

With the use of keywords, a comprehensive literature search retrieved a total of 311 documents, from which 18 were finally selected through screening. We conducted a systematic review of these, but there were no documents directly examining the outcome related to this CQ. The extracted documents consisted of post hoc analyses of RCTs for mCSPC and retrospective analyses of small single-treatment groups.

SR results

O1: Extension of overall survival: There were limited documents allowing the review of the outcome, and only one report of a retrospective analysis existed.[157] It has been reported that the median overall survival of the patient population who received abiraterone or enzalutamide as a first-line treatment after progression to mCRPC in the patient group treated with DTX for mCSPC was longer than that of the patient population who received other treatments (including DTX and cabazitaxel). There were no reports on CRPC after the upfront ARSI. Therefore, both the effect size and strength of evidence were judged to be not assessable.

O2: Maintained QOL: It was impossible to find documents related to the maintenance of QOL-targeting patients who received treatment for mCRPC after upfront mCSPC treatment. Therefore, both the effect size and strength of evidence were judged to be not assessable.

O3: Extension of radiographic progression-free survival: In the retrospective study results of patients who received upfront DTX treatment for mCSPC, the median duration of radiographic progression-free survival was 9.0 months for patients who were treated with abiraterone or enzalutamide as a first-line treatment for mCRPC at the time of progression, whereas it was 3.0 months for the group that received other treatment drugs (including DTX and cabazitaxel).[158] Incidentally, there was no report on CRPC after the upfront ARSI. Therefore, both the effect size and strength of evidence were judged to be not assessable.

O4: Prevention of skeletal-related events: No reports of direct comparisons of DTX or ARSI in the treatment of

TABLE 28 Committee vote results of CQ13.

Strongly recommended	Weakly recommended	Weakly recommended not to do	Strongly recommended not to do	No recommendation	Abstention (for COI)
0 (0%)	1 (8.3%)	0 (0%)	0 (0%)	11 (91.7%)	6

TABLE 29 Components of the CQ13: P (Patients): mCRPC patients after the upfront therapy (ARSI/DTX) for mCSPC; I (Interventions): Unused ARSI + ADT; C (Comparisons, Controls): DTX + ADT; O (Outcomes): (see below).

	Outcome	Benefit/harm	Importance (points)	Effect of intervention on outcome	Strength of evidence
O1	Extension of overall survival	Benefit	9	Not assessable	Not assessable
O2	Maintained QOL	Benefit	8	Not assessable	Not assessable
O3	Extension of radiographic progression-free survival	Benefit	7	Not assessable	Not assessable
O4	Prevention of skeletal-related events	Benefit	7	Not assessable	Not assessable
O5	Increase in medical expenses	Harm	6	Not assessable	Not assessable
O6	Adverse events	Harm	7	Not assessable	Not assessable

mCRPC after upfront therapy for mCSPC for skeletal-related events have been published, and no papers have been published evaluating the treatment of single groups. Consequently, both the effect size and strength of evidence were judged to be not assessable.

O5: Increase in medical expenses: No reports of direct comparisons between DTX and ARSI in the treatment of mCRPC after upfront therapy for mCSPC in relation to the increase in medical expenses have been published, and no papers have been published evaluating the treatment of single groups. Therefore, both the effect size and strength of evidence were judged to be not assessable.

O6: Adverse events: One report on the incidence of adverse events caused by DTX or ARSI as a primary treatment for mCRPC after upfront DTX exists. However, since there are no reports on CRPC after upfront ARSI, it was concluded that both the effect size and strength of evidence were judged to be not assessable.

Balance between benefits and harms

Regarding the benefits of "extension of overall survival" (O1) and "extension of radiographical progression-free survival" (O3), a few retrospective observational studies have indicated better results from administering ARSI to mCRPC following upfront DTX than other therapies, but sufficient evidence levels have not been met. The literature assessing other outcomes is scant. Additionally, it is currently unreported for mCRPC following upfront ARSI, which is expected to be used more in Japan in the future. Consequently, the superiority or inferiority of DTX or unused ARSI as primary treatment for mCRPC following upfront therapy (ARSI or DTX) is unclear, with selection based on the patient's condition and preferences. However, the accumulation and analysis of real-world data in the future are deemed to be extremely important and appropriate as a future research subject.

Values, preferences, and burden of patients

When choosing between cytotoxic chemotherapy and hormone therapy, ignoring patient preferences and opinions is impossible. Also, individual patients' general health typically dictates whether they are suitable for each treatment. Although high-quality literature relating to this CQ was impossible to find, it was deemed fair to select a medication according to the patient's condition and preferences in the current situation, as it is unclear whether DTX or unused ARSI is superior as the primary treatment for mCRPC following upfront therapy (ARSI or DTX) for mCSPC.

Cost and resource use

Generally, the values of patients who are averse to the side effects of cytotoxic chemotherapy should be respected, but the out-of-pocket expenses for ARSI treatments may also pose a significant issue. Therefore, it is preferable to select which medical resources to use after thoroughly the patient's wishes and preferences.

Recommendations development

There is no surrounding evidence regarding this CQ, as the effectiveness of upfront therapy was recently proven. Therefore, it is inevitable that the decision will be to have no recommendation in the present guideline. All guideline committee members consistently agreed that the building and accumulation of future evidence relating to this CQ are required.

CQ14: Should radium-223 dichloride (Ra-223) be co-administered when using novel androgen receptor-signaling inhibitors (ARSIs) for castration-resistant prostate cancer (CRPC) (visceral metastasis-free and bone metastatic)?

Recommendation: It is weakly recommended not to co-administrate Ra-223 when using ARSIs for CRPC due to the increased risk of bone fractures.

[Level of Recommendation: Weak recommendation; Strength of Evidence: C (weak)] (Tables 30 and 31).

Background

In the treatment of mCRPC with bone metastasis, the ALSYMPCA study (Ra-223 vs. placebo) demonstrated that Ra-223 extended overall survival and delayed time to skeletal-related events.[159] A Phase IIIb early access trial conducted after the ALSYMPCA study saw an extension of overall survival in patients who received concurrent treatment with Ra-223 and either abiraterone or enzalutamide.[160] ARSI has proven effective against mCRPC, and further augmented effects are expected when combined with Ra-223.

Literature search

A comprehensive literature search was conducted using 10 keywords (Radium 223, enzalutamide, abiraterone acetate, castration-resistant prostate cancer, bone metastasis, bone-modifying agent, fracture, osteonecrosis of the jaw, skeletal-related event, and prostate-specific antigen) and 3 key papers[159–161] for this CQ. This resulted in the extraction of

TABLE 30 Committee vote results of CQ14.

	Strongly recommended	Weakly recommended	Weakly recommended Not to Do	Strongly recommended not to do	Abstention (For COI)
1st Vote	0 (0%)	3 (21.4%)	10 (71.5%)	1 (7.1%)	4
2nd Vote	0 (0%)	0 (0%)	13 (86.7%)	2 (13.3%)	4

TABLE 31 Components of the CQ14: P (Patients): CRPC patients (visceral metastasis-free and bone metastatic); I (Interventions): Ra-223 + ARSI; C (Comparisons, Controls): ARSI; O (Outcomes): (see below).

	Outcome	Benefit/harm	Importance (points)	Effect of intervention on outcome	Strength of evidence
O1	Extension of overall survival	Benefit	9	No effect	C (Weak)
O2	Extension of radiographic progression-free survival	Benefit	8	No effect	C (Weak)
O3	Decreased PSA level	Benefit	5	No effect	C (Weak)
O4	Decreased ALP level	Benefit	5	No effect	C (Weak)
O5	Improved QOL	Benefit	7	No effect	C (Weak)
O6	Prevention of symptomatic skeletal-related events	Benefit	7	Small inverse effect	C (Weak)
O7	Adverse events	Harm	8	Small effect	C (Weak)

156 articles from PubMed and 11 articles from Ichushi-Web. After primary screening, the number was reduced to 14 papers, and after a second screening, it was finally narrowed down to 13.

SR results

O1: Extension of overall survival: The outcome was evaluated to see if the addition of Ra-223 to ARSI extended overall survival. The EORTC-1333-GUCG (PEACE III) study, which examined concurrent treatment with enzalutamide and Ra-223, has not yet been published. Therefore, the results indicating overall survival only come from the ERA223 study, which investigated concurrent treatment with abiraterone and Ra-223. The data from the entire ERA223[161] and the Japanese portion[162] were the target of the review. The median overall survival in the entire ERA223 study was 33.3 months for the abiraterone + placebo group and 30.7 months for the abiraterone + Ra-223 group (hazard ratio: 1.195, 95% CI: 0.950–1.505).[161] In Japan, no significant difference was observed, with the overall survival time of the abiraterone + placebo group being 30.3 months and the overall survival time for the abiraterone + Ra-223 group not reaching the median.[162] Therefore, co-administration of Ra-223 and ARSIs was judged to have no effect on O1 in either the overall study or the Japanese portion of the study. As there was only one RCT, the strength of evidence was rated as C (weak).

O2: Extension of radiographic progression-free survival: In the ERA223 study, the median radiographic progression-free survival was 12.4 months for the abiraterone + placebo group and 11.2 months for the abiraterone + Ra-223 group. No extension of radiographic progression-free survival was observed (hazard ratio: 1.152, 95% CI: 0.960–1.383).[161] No extension of radiographic progression-free survival was observed in the Japanese portion of the ERA223 study for the group treated with abiraterone + Ra-223.[162] Therefore, co-administration of Ra-223 and ARSIs was judged to have no effect on O2 in any study, and as there was only one RCT, the strength of evidence was considered C (weak).

O3: Reduced PSA levels: In the ERA223 study, the decrease in PSA levels (defined as a reduction of 30% or more from baseline) was 72% in the abiraterone + Ra-223 group and 67% in the abiraterone + placebo group.[161] Furthermore, no extension of the time for PSA progression was observed with the abiraterone + Ra-223 group.[161] Therefore, co-administration of Ra-223 and ARSIs was judged to have no effect on O3, and the strength of evidence was rated as C (weak) due to it being based on a single RCT.

O4: Reduction in ALP levels: In the ERA223 study, the rate of decrease in alkaline phosphatase (ALP) levels (defined as a reduction of 30% or more from the baseline) was 55% in the abiraterone + Ra-223 group and 26% in the abiraterone + placebo group.[161] Additionally, no significant difference was found in the median time to ALP progression, with 7.4 months in the abiraterone + Ra-223 group and 6.8 months in the abiraterone + placebo group (hazard ratio: 1.083, 95% CI: 0.918–1.276).[161] Therefore, co-administration of Ra-223 and ARSIs was judged to have no effect on O4, and the strength of evidence was rated as C (weak) due to it being based on a single RCT.

O5: Improved QOL: In the ERA223 study, the time to deterioration in health-related quality of life (HRQOL) (defined as a drop of 2 points in the physical disease-related symptoms subscale score in two consecutive evaluations at least 4 weeks apart) was not significantly different between the abiraterone + Ra-223 group (9.5 months) and the abiraterone + placebo group (10.5 months).[161] Therefore, co-administration of Ra-223 ARSIs was judged to have no effect on O5, and the strength of evidence was rated as C (weak) due to it being based on a single RCT.

O6: Prevention of symptomatic skeletal-related events: We evaluated whether the additional administration of Ra-223 with ARSI had a preventive effect on symptomatic skeletal-related events. In the overall ERA223 study, the median time to the occurrence of symptomatic skeletal-related events was 26.0 months in the abiraterone + placebo group and 22.3 months in the abiraterone + Ra-223 group (hazard ratio: 1.122, 95% CI: 0.917–1.374).[161] No extension of the time to the emergence of symptomatic skeletal-related events was observed with the combination of abiraterone and Ra-223 in either the entire cohort or the Japanese cohort. The ERA223 study showed a 29% fracture rate in the abiraterone + Ra-223 group and an 11% fracture rate in the abiraterone + placebo group,[161] which was harmful, contrary

to the expected effect. Based on these results, and given the higher fracture rate in the Ra-223 combination group, the co-administration of Ra-223 and ARSIs was judged to have a "Small inverse effect," and the strength of evidence was rated as C (weak) due to it being based on a single RCT.

O7: Adverse events: We evaluated whether the administration of Ra-223 in addition to ARSI would increase adverse events. In the ERA223 study, 41% of the abiraterone + Ra-223 group and 39% of the abiraterone + placebo group experienced serious treatment-related adverse events. Also, 29% of the abiraterone + Ra-223 group and 11% of the abiraterone + placebo group experienced fractures. In the abiraterone + Ra-223 group, non-bone metastasis sites were the most common site of fractures at 79%, and osteoporotic fractures were the most common type at 49%.[161] In the ERA223 study, a decrease in fracture risk was observed in patients who received bone-modifying agents (BMAs). As a result, the use of BMAs was mandated in the PEACE III trial, comparing the enzalutamide + Ra-223 group with the enzalutamide monotherapy group.[163] Although only one high-quality intervention study exists, the fracture rate was higher in the Ra-223 combination group in relation to O7. However, the use of BMAs could possibly prevent this adverse event, which was judged as having a "Small effect." The strength of evidence was rated as C (weak) due to it being based on a single RCT.

Balance between benefits and harms

The Ra-223 + abiraterone group showed no effect when compared to the abiraterone monotherapy group in beneficial outcomes, such as "extension of overall survival" (O1), "extension of radiographic progression-free survival" (O2), "decreased PSA levels" (O3), "decreased ALP levels" (O4), and "improved QOL" (O5). Another beneficial outcome, "prevention of symptomatic skeletal related events" (O6), conversely resulted in a higher fracture rate in the combination group. In terms of the harm of "adverse events" (O7), the results in the combination group were worse. As no benefits were observed and harms were identified, it was decided to recommend not to do co-administration of Ra-223 + abiraterone.

However, in the PEACE III trial, where the Ra-223 + enzalutamide combined group was compared with the enzalutamide monotherapy group, it was reported that the risk of fractures was reduced by combining with BMAs, although these results have not yet been published. The final report is awaited.

Values, preferences, and burden of patients

Ra-223 and ARSI both have high costs, so there is a clear increase in expenses due to combination therapy. ARSIs are widely used and are generally well received for patients with CRPC, but Ra-223 is not as commonly used due to difficulties in use timing.

Cost and resource use

Based on the above results, the Japanese packet insert for Ra-223 states, "Co-administration of Ra-223 and abiraterone is not recommended for patients with bone metastasis from castration-resistant prostate cancer."

Recommendations development

No effect was observed for the four pivotal beneficial outcomes, and only a minor effect was observed for one serious harm. The strength of evidence was rated as C (weak) for all. It is also stated in the packet insert that "Co-administration of Ra-223 and abiraterone is not recommended." On the other hand, it has been reported that the risk of fractures is reduced by combining BMAs with Ra-223 and another ARSI, enzalutamide. Finally, based on an 86.7% vote, it was decided to "Weakly recommend not to do the combination of Ra-223 and ARSI because it increases the risk of fractures."

ALGORITHMS

The recommendations for the 14 CQs were finalized, and the results were combined to create the following five algorithms.

1 Algorithm for diagnosis (Figure 1).
2 Algorithm for localized and locally advanced prostate cancer treatment (Figure 2).
3 Algorithm for metastatic castration-sensitive prostate cancer (mCSPC) treatment (Figure 3).
4 Algorithm for non-metastatic castration-resistant prostate cancer (nmCRPC) treatment (Figure 4).
5 Algorithm for castration-resistant prostate cancer (mCRPC) treatment (Figure 5).

GENERAL STATEMENT

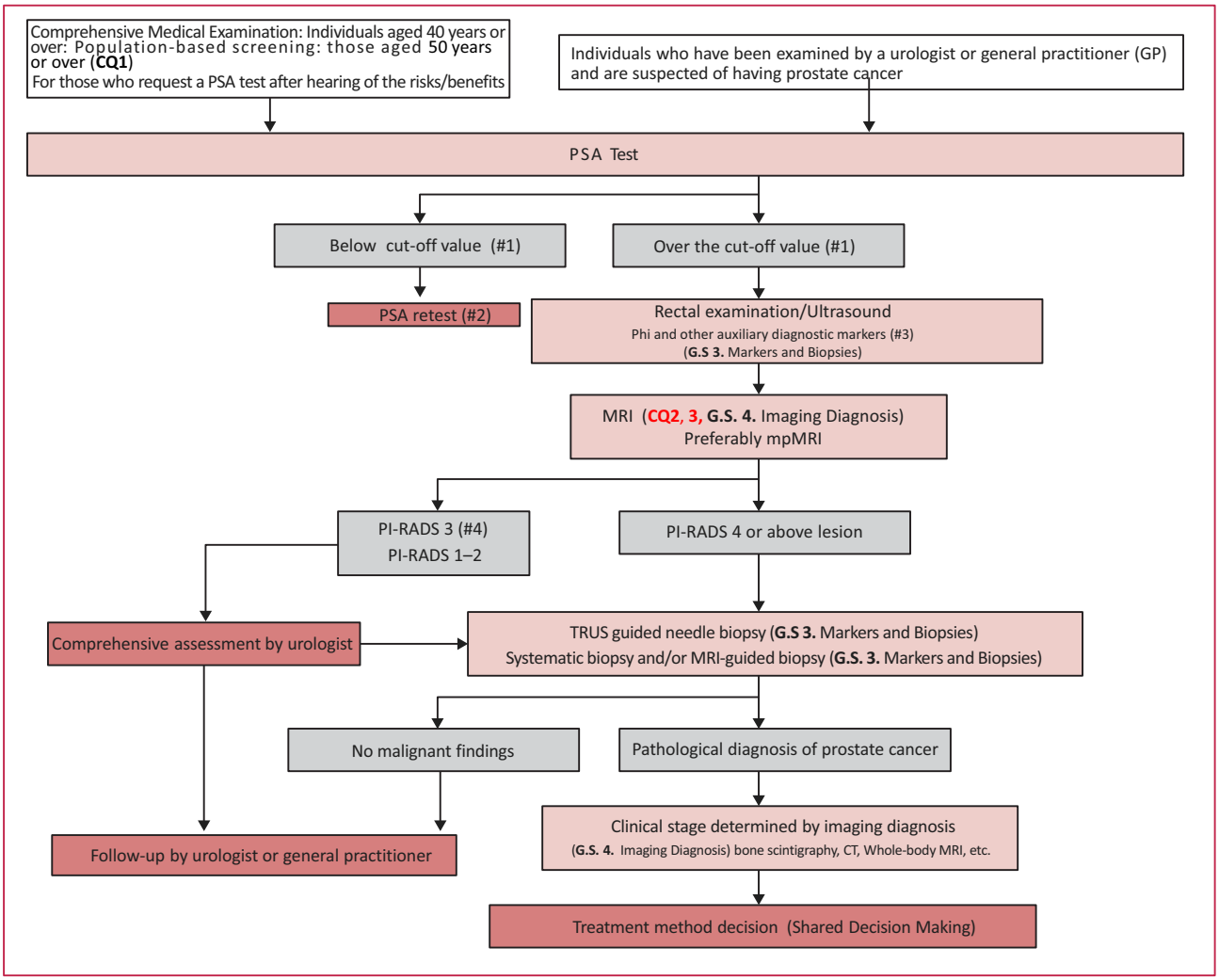
This general statement describes a general discussion of textbook content not covered in the SR. We listed roughly 5 main points for each of the 14 areas and selected about 10 keywords and 2–3 key reference papers for each of these points. Based on the above, we formulated a search formula and conducted a literature search. We primarily documented findings made clear after the content of the general statement and the CQs of the Clinical Practice Guidelines for Prostate Cancer 2016.

Epidemiology

We provided an overview of the morbidity and mortality rates of prostate cancer and predictions for the future. We also discussed the congenital and genetic factors and acquired factors as prostate cancer risks. Furthermore, we described the prevention of prostate cancer and trends in latent prostate cancer.

Screening

We indicated that having a family history of prostate cancer increases the risk. We recommend screening for prostate cancer for individuals from the age of 50 and at personal expense through general health checks from the age of 40. We mentioned drugs that affect PSA values, such as 5α-



G.S., General statement; Phi, prostate health index; mpMRI, multiparametric MRI; PI-RADS, Prostate Imaging Reporting and Data System

#1: The recommended PSA cut-off value is 4.0 ng/mL for all ages. The cut-off value by age group (50–64: 3.0 ng/mL, 65–69: 3.5 ng/mL, 70 or over: 4.0 ng/mL) can also be used. (2018 Prostate Cancer Screening Guidelines).

#2: For individuals with a PSA cut-off value of 1.0 ng/mL or below, the recommended interval of screening tests is three years, while an annual test is recommended for individuals with a PSA cut-off value of 1.1 ng/mL or above (2018 Prostate Cancer Screening Guidelines).

#3: Auxiliary diagnostic markers for the cases over the PSA cut-off value include phi, PCA3, 4k-panel, and S2, 3PSA%. At the time of publication of these clinical guidelines, only phi is covered by insurance (**G.S. 3.** Markers and Biopsies).

#4: For PI-RADS 3 lesion biopsies, it is necessary to thoroughly examine risk factors, including PSA density (PSAD).

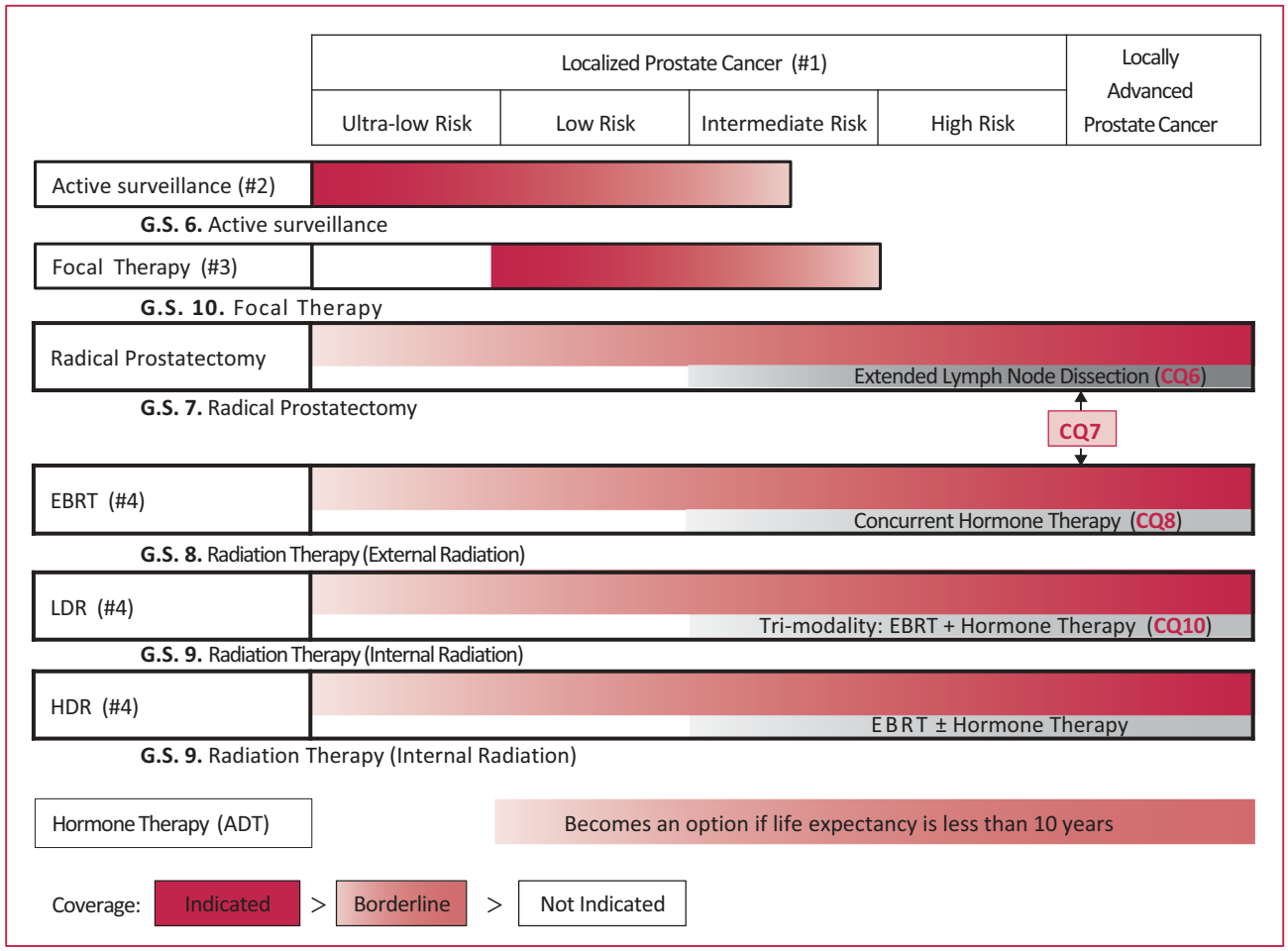
FIGURE 1 Algorithm for diagnosis.

reductase. Regarding the cut-off value and measurement interval of PSA, please refer to the algorithm related to diagnosis. We also discussed how screening is handled in overseas guidelines such as AUA and EAU.

Markers and biopsies

We mentioned auxiliary diagnostic markers other than PSA (PCA3, 4 k-panel, phi, S2, and 3PSA%). Phi is calculated by multiplying the ratio occupied by [−2] proPSA, a precursor of PSA, in fPSA by the square root of total PSA and is expressed as phi = ([−2] proPSA / fPSA) X$\sqrt{}$(tPSA). Phi has been shown to be useful in detecting clinically significant cancers, even in prospective studies targeting Japanese populations[164], and was added to insurance coverage in November 2021.

Regarding biopsies, we described the types and usefulness of MRI-targeted biopsies (MTB) and whether a combination



G.S., General statement; EBRT, external beam radiation therapy; LDR, low dose rate brachytherapy; HDR, high dose rate brachytherapy; ADT, Androgen deprivation therapy

#1: Risk classification was based on the NCCN risk classification (**Appendix 3**). NCCN uses a category of ultra-high risk above high risk, but these guidelines use locally advanced prostate cancer instead of ultra-high risk. Since the intermediate-risk group has been pointed out for its heterogeneity in treatment outcomes, NCCN defines prognostically favorable intermediate risk and prognostically unfavorable intermediate risk. However, as only the limited literature cited in these guidelines uses this definition, it was not used in this algorithm to avoid confusion.

#2: The "Prostate Cancer Screening Guidelines 2016" used "PSA ≤10 ng/mL, clinical stage ≤ pT2, number of positive cores ≤ 2 (however, this does not apply in the case of target biopsy or saturation biopsy), Gleason score ≤ 6, and further, PSA density (PSAD) < 0.2 or < 0.15 ng/mL/mL" as eligibility criteria. In this revision (**CQ5**), new eligibility criteria were added, and it was decided to add "weakly recommend active surveillance therapy for patients who have a Gleason score of 3 + 4 or less, two or fewer positive core numbers, PSA 10 ng/mL or less, PSAD < 0.2 ng/mL/mL, not including cribriform or intraductal carcinoma, among intermediate-risk prostate cancers."

#3: Focal therapy is indicated when grade group [classification] (GG) 2 or 3 is detected from lesions visualized on multiparametric MRI (mpMRI) or when the lesion is large, even if it is GG 1.

#4: In terms of EBRT, LDR or HDR monotherapy is indicated for some low-risk to intermediate-risk cases.

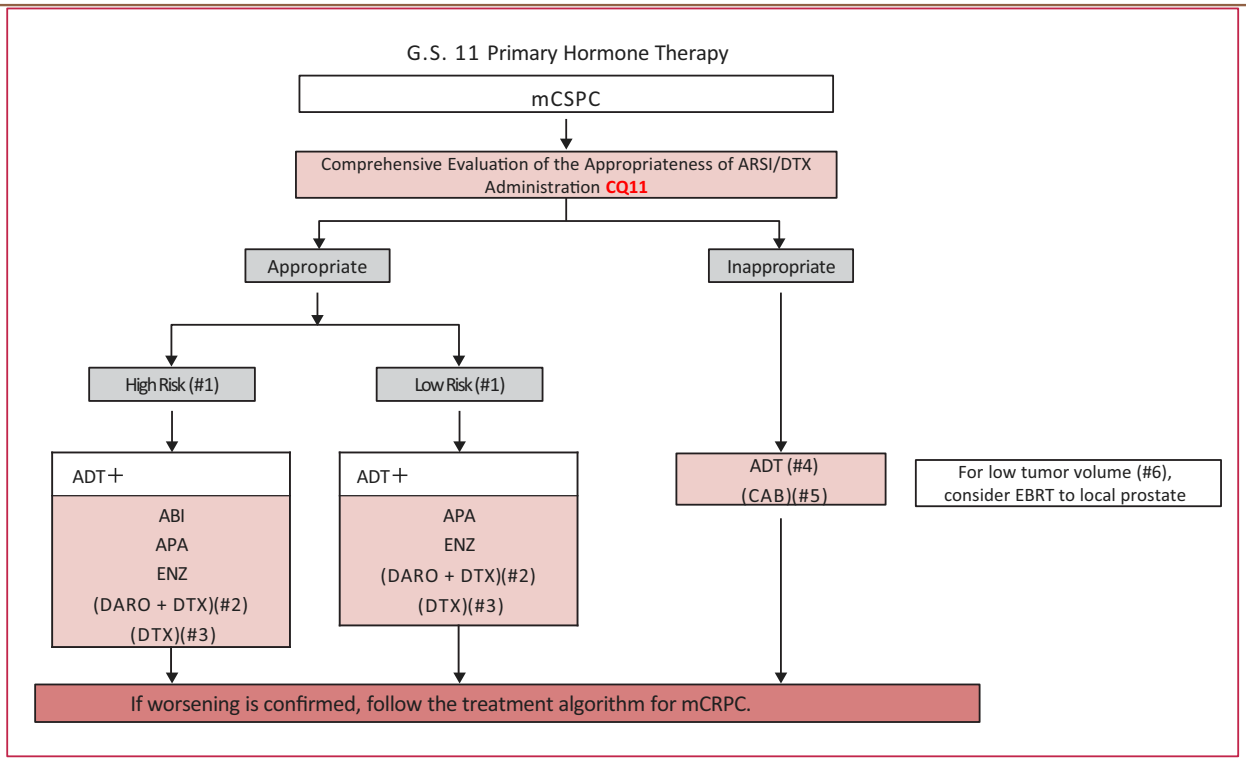
FIGURE 2 Algorithm for localized and locally advanced prostate cancer treatment.

of transrectal ultrasonography-guided systematic biopsy (TRUS-guided SB) and MTB should be performed.

Imaging diagnosis

The use of 3 Tesla MRI in imaging diagnosis of localized prostate cancer, particularly the ability to capture with high b-values of 2000 s/mm^2 in DWI, is emphasized. For a comparison of mpMRI and bpMRI, please refer to CQ3. Changes in PIRADS v2.1 are described in detail.

The accuracy of currently used MRI and CT in lymph node diagnosis is not satisfactory, and we await the clinical introduction of PSMA-PET. The usefulness of whole-body MRI (already covered by insurance) and PSMA-PET (not yet



G.S., General statement; ARSI, Novel androgen receptor signaling inhibitor; ADT, Androgen deprivation therapy; CAB, Combined androgen blockade; EBRT, external beam radiation therapy; ABI, Abiraterone; APA, Apalutamide; ENZ, Enzalutamide; DARO, Darolutamide; DTX, Docetaxel

#1: The risk classification was based on the definition from the LATITUDE trial. That is, mCSPC with at least two of the following – a Gleason score of 8 or more, three or more osseous lesions as per bone scintigraphy, or visceral metastasis – were defined as high risk. Anything not meeting these criteria was defined as low risk.

#2: In a randomized controlled trial (RCT), it was shown that the triplet therapy of androgen deprivation therapy (ADT) with DARO and DTX prolongs overall survival compared with ADT plus DTX. Although it was covered by insurance as of February 2023, there is a lack of data in clinical practice, and further analysis of treatment outcomes is required (**CQ11** Future Research).

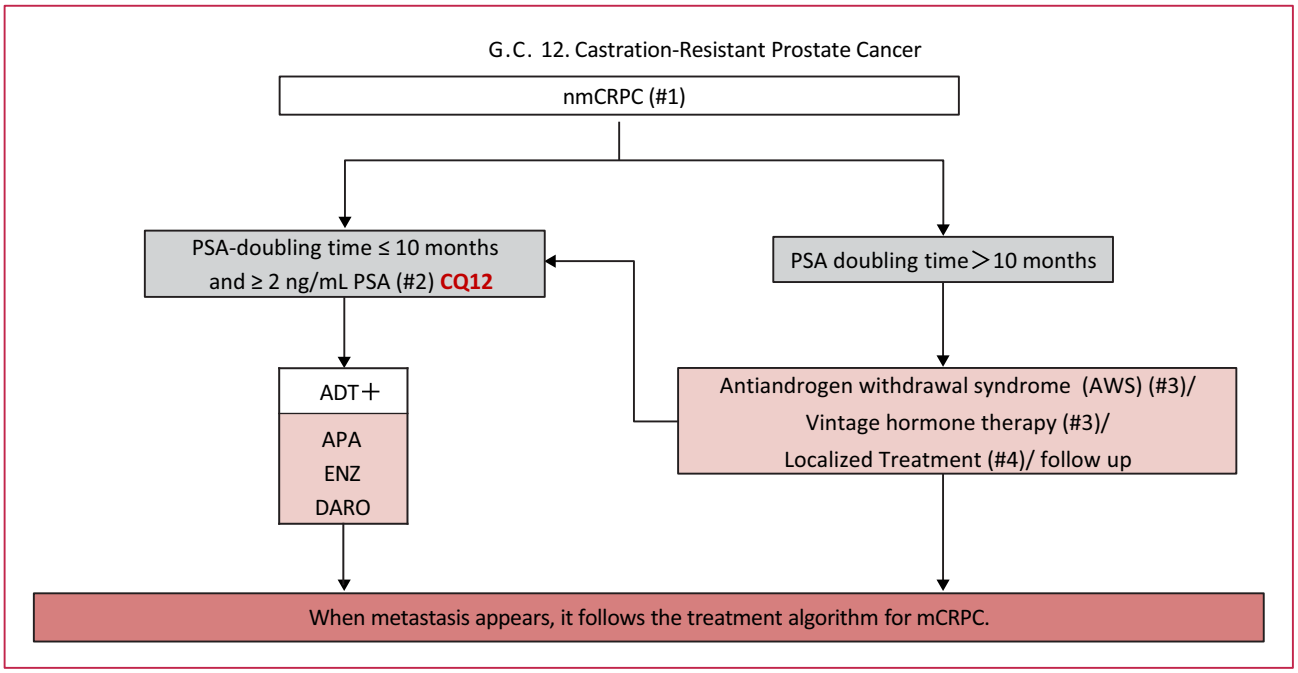
#3: As a result of the **CQ11** network meta-analysis, it was weakly recommended to adopt the new androgen receptor signaling inhibitor (ARSI) rather than using docetaxel.

#4: For ADT, there are luteinizing hormone-releasing hormone (LH-RH) agonists, LH-RH antagonists, and surgical castration. Intermittent hormone therapy may be considered when adverse events due to ADT become problematic (**G.S. 11.** Primary Hormone Therapy).

#5: Combined androgen blockade (CAB) therapy is a method that adds vintage hormone therapy using agents such as bicalutamide or flutamide to ADT (implying hormone therapy from the era prior to ARSI). Considering the lack of evidence demonstrating superiority over ADT alone, the text in parentheses is included (**G.C. 11.** Primary Hormone Therapy).

#6: For the indication of EBRT for the local prostate, the definition of low tumor volume in the CHAARTED trial should be taken into account. In the CHAARTED trial, visceral metastasis or four or more than four osseous metastases (with at least one in the spine or outside the pelvis) were defined as high tumor volume, and any other diseases were defined as low tumor volume. For EBRT to the local prostate in low volume mCSPC cases, an improvement in overall survival effect was reported on a sub-group analysis basis, and this consideration is included.

FIGURE 3 Algorithm for metastatic castration-sensitive prostate cancer (mCSPC) treatment.



ADT, Androgen deprivation therapy; APA, Apalutamide; ENZ, Enzalutamide; DARO, Darolutamide

#1: The concept of nmCRPC did not exist when the 2016 edition of treatment guidelines was published. It is defined as a state of CRPC in which, despite undergoing ADT, a rise in PSA values is observed, and no distant metastasis can be detected through conventional imaging examinations such as bone scintigraphy, CT scans, or MRI. There are two patterns: one where the disease advances after ADT following radical treatment such as surgery or radiotherapy, and another where the disease advances after conducting ADT without local treatment.

#2: Based on the registration criteria of clinical trials for apalutamide, enzalutamide and darolutamide.

#3: If CAB was carried out as the first-line treatment, discontinuing vintage hormones such as bicalutamide or flutamide might improve the disease condition, including a decrease in PSA levels. This is referred to as anti-androgen withdrawal syndrome (AWS). Also, adding vintage hormones in cases where ADT was the primary treatment may similarly improve disease conditions.

As noted in point #5 of **3. Algorithm for mCSPC treatment**, with ARSI becoming the mainstay of treatment, such vintage hormones are no longer widely used. Therefore, vintage hormones were not discussed in the main text of the current treatment guidelines.

#4: If local treatment was not conducted as an initial treatment, it should also be considered.

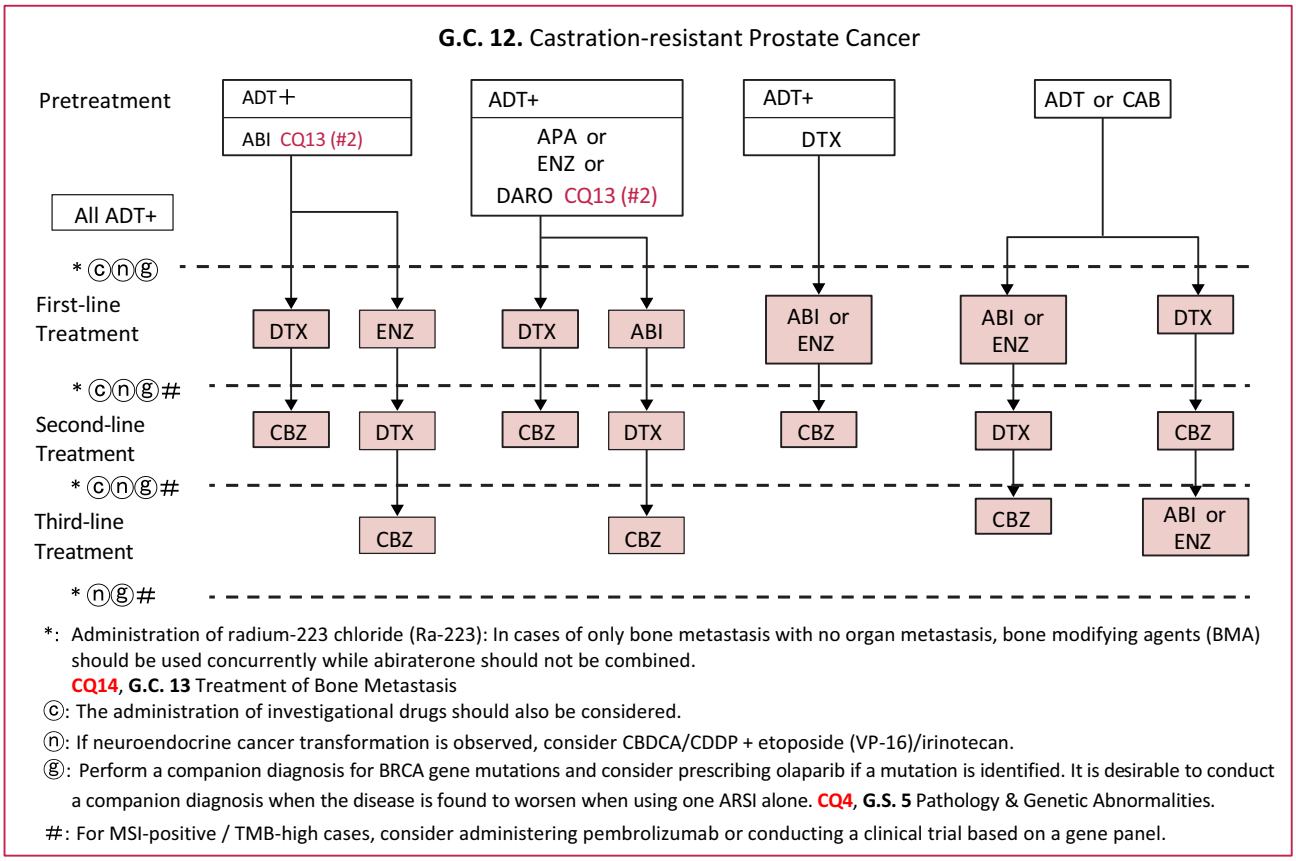
FIGURE 4 Algorithm for non-metastatic castration-resistant prostate cancer (nmCRPC) treatment.

covered by insurance) is mentioned in relation to bone metastasis.

Pathology and Genetic Abnormalities

Discussions are held regarding issues with the Gleason grading system in the pathological diagnosis of prostate cancer and the newly proposed grade group (GG) classification. Furthermore, the importance of intraductal carcinoma of the prostate (IDC-P) with invasive components as a poor prognosis factor, its position in foreign guidelines, and its positioning in the Japanese prostate cancer handling rules are mentioned.

Regarding genetic disorders, it is mentioned that the TMPRSS2 (a prostate-specific, androgen-responsive, transmembrane serine protease gene): ERG fusion gene is an early



ADT, Androgen deprivation therapy; CAB, Combined androgen blockade; ARSI, Novel androgen receptor signaling inhibitor
G.S., General statement; ABI, Abiraterone; APA, Apalutamide; DARO, Darolutamide; ENZ, Enzalutamide; DTX, Docetaxel, CBZ: cabazitaxel

#1: It has been decided not to mention choices of treatment in the event of transitioning to CRPC after triplet therapy (a combination of three drugs) utilizing DARO and DTX in ADT due to the lack of substantial evidence.

#2: It remains unclear whether the as yet unused ARSI and DTX are superior in the first-line treatment of mCRPC after upfront therapy (novel ARSI/DTX) for mCSPC. It would be preferable to select a treatment based on the patient's condition and preferences (**CQ13**).

FIGURE 5 Algorithm for castration-resistant prostate cancer (mCRPC) treatment (#1).

phenomenon in the carcinogenesis of prostate cancer. Also, an example of the DNA damage repair mechanism is homologous recombination repair (HRR), and the group of genes responsible for this double-strand repair (HRR-related genes) includes *BRCA1/2*, *ATM*, and *CDK12*. For *BRCA1/2* gene abnormalities, olaparib, a PARP inhibitor, is useful—the details of which can be found in CQ4. Genetic abnormalities in hereditary prostate cancer, including *BRCA1/2* and *HOXB13* mutations, are also highlighted.

Active surveillance

Based on the studies comparing the prognosis of patient groups undergoing active surveillance and those receiving curative treatments, such as surgery or radiation, for localized prostate cancer, active surveillance is recommended for early prostate cancer to prevent overtreatment, as there was no difference between the two groups[165,166]. Although previously recommended for low-risk prostate cancer, the pros and cons of active surveillance for intermediate-risk groups have recently been debated. Foreign guidelines do not recommend active surveillance for poor prognosis intermediate-risk groups, but there are those with good prognosis in the intermediate-risk group that are candidates for active surveillance. Refer to CQ5.

The use of MRI and various markers to further improve the accuracy of active surveillance is also discussed.

Radical prostatectomy

In terms of techniques, robotic-assisted radical prostatectomy (RARP) is equivalent in terms of cancer control to traditional retropubic radical prostatectomy (RRP) but has advantages such as lesser bleeding and a shorter hospital stay, and it has been widely performed in Japan.

According to the 2016 Clinical Practice Guidelines for Prostate Cancer, radical prostatectomy is recommended with Grade A for low- to intermediate-risk prostate cancer with an

expected life span of more than 10 years. For details regarding the application of radical prostatectomy in high-risk prostate cancer cases, please see CQ7, under the comparison with hormonal therapy combined with radiotherapy.

Many studies have been conducted on how to preserve urinary and sexual function after radical prostatectomy. Factors affecting postoperative sexual function include age and preoperative erectile function. The level of nerve preservation is the only proven surgeon-related factor. As for postoperative urinary incontinence, many factors like age, obesity, comorbidities, and membranous urethral length are involved, and the important surgeon-related factors are preservation of the urethral sphincter and nerve preservation.

Radiation therapy (external beam radiation therapy)

External beam radiation therapy for localized prostate cancer has been established as an effective therapy based on numerous large prospective RCTs. Although a dose–response relationship with tumor control rates is observed in the dose range of 140 Gy (equivalent to 60 Gy in 30 fractions) to 190 Gy (equivalent to 80 Gy in 40 fractions) with BED1.5 (biologically effective dose when the α/β value is 1.5 Gy), it is known to plateau with doses over 200 Gy BED1.5. Thus, it is important to judiciously combine hormonal therapy to improve treatment effects. For details, refer to CQ8.

Hypofractionation (HF) requires fewer sessions and is more convenient for patients than a conventional fraction (CF), but as it requires increased irradiation dosages per session, it requires image-guided radiotherapy (IGRT) to increase irradiation accuracy. For a comparison of HF and CF, please refer to CQ9a, b.

Despite not outperforming traditional external beam radiation therapy, particle beam therapy is evaluated as equivalent and has been covered by insurance since April 1, 2018. Based on the subanalyses of several clinical trials, additional external beam radiation therapy to the local prostate site in mCSPC patients has been suggested to be more useful in patients with fewer metastases. The results of a large prospective clinical trial (PEACE1 trial) are awaited.

Radiation therapy (internal radiation)

Two methods of brachytherapy for prostate cancer exist: low dose rate (LDR) and high dose rate (HDR). In Japan, there are more facilities that perform LDR brachytherapy than HDR brachytherapy.

LDR brachytherapy is normally performed alone in low-risk prostate cancer, while in high-risk cases, it is combined with EBRT or with EBRT and hormonal therapy (tri-modality). Please refer to CQ10 for tri-modality results. LDR brachytherapy has generally good long-term treatment results.

Most HDR brachytherapy is used together with EBRT, primarily for the treatment of high-risk prostate cancer. Initially used as an adjunct to EBRT, HDR brachytherapy also began to be used as a stand-alone therapy. Low to relatively low malignant intermediate-risk prostate cancer is often treated with HDR brachytherapy alone, and relatively high malignant intermediate- to high-risk prostate cancer is often indicated for EBRT + HDR.

Focal therapy

Focal therapy is a new surgical treatment aimed at avoiding erectile dysfunction and urinary incontinence, which are complications after radical prostatectomy. It specifically includes cryotherapy, high-intensity focused ultrasound (HIFU), brachytherapy, and vascular-targeted photodynamic therapy (VTP). Among these, only brachytherapy is covered by insurance in Japan, while the other treatments are administered within the scope of clinical trials aiming to achieve insurance coverage.

The prostate cancer targeted by focal therapy is clinically significant cancer, which is quite different from that targeted by active surveillance (see the treatment algorithm for localized and locally advanced prostate cancer). Focal therapy targets cases where GS7 or higher (GG2 or higher) is detected from targeted biopsy tissue taken from lesions visualized in imaging examinations, such as mpMRI, of localized prostate cancer, or where it is considered clinically significant cancer because it is high volume even if it is GS6 (GG1). The biggest problem in validating focal therapy is the method of determining the effect of treatment, and it is difficult to compare focal therapy, where the prostate itself is preserved, with traditional surgery or radiation therapy. Against this backdrop, the Guidelines for Clinical Trial to Evaluate Medical Devices for Focal Therapy of Prostate Cancer was published in 2021 by the Japanese Urological Association. It is expected that pharmaceutical devices will be assessed based on standards and evaluation methods in line with the newly proposed guidelines, and new evidence will be created on the basis of treatment results from mid- to long-term cancer control using focal therapy.

Primary hormone therapy

In Japan, combined androgen blockade (CAB) therapy, where surgical or chemical castration (luteinizing hormone-releasing hormone (LHRH) agonist) is combined with anti-androgen drugs, has been widely used for progressive prostate cancer. Although some reports concluded the superiority of CAB therapy over androgen deprivation therapy (ADT) alone, with the introduction of the below-mentioned docetaxel (DTX) and novel ARSI combination therapy as the standard treatment, the significance of CAB therapy is diminishing.

Since 2013, three RCTs that tested the effectiveness of DTX combined with castration monotherapy for metastatic castration-sensitive prostate cancer (mCSPC) and two trials reported that the combination with DTX significantly prolonged overall survival. In 2017, it was reported that combining castration monotherapy with abiraterone significantly extended overall survival for mCSPC with high-risk factors. In addition, in 2019, it was reported that combining castration monotherapy with apalutamide or enzalutamide extended overall survival for all mCSPC. Furthermore, two RCTs have reported that combining DTX and ARSI with castration therapy significantly extended overall survival compared with the

combination of DTX and a placebo, and of these, combined treatment with castration, DTX, and darolutamide is covered by insurance in Japan as of February 2023. For these combination treatments, please refer to CQ13 to decide whether to use DTX or ARSI.

Introduced in 2012, LHRH antagonists have the advantage of being able to avoid the transient testosterone surge, or flare-up phenomenon, seen with LHRH agonists. Because of their rapid testosterone inhibitory effect, they are desirable in cases where there is the potential for imminent complications, such as spinal cord compression. Whether LHRH antagonists are superior to LHRH agonists in terms of long-term therapeutic effects and adverse events requires further verification.

Castration-resistant prostate cancer

Castration-resistant prostate cancer (CRPC) is currently divided into non-metastatic CRPC (nmCRPC) and metastatic CRPC (mCRPC). For the usefulness of ARSI for nmCRPC, please refer to CQ12 and Algorithm 4.

For mCRPC, the treatment options for cases of CRPC when ADT alone or CAB therapy was the standard treatment now include DTX, ARSI (abiraterone and enzalutamide), cabazitaxel, Ra-223, and olaparib (see Algorithm 5). Additionally, pembrolizumab may be considered for cases with microsatellite instability (MSI) test-positive or high TMB. Cabazitaxel significantly extended overall survival for DTX-resistant CRPC, but neutropenia frequently occurred, so preventive administration of granulocyte colony-stimulating factor (G-CSF) is recommended. The issue is the sequence in which these treatments are used. From the perspective of cross-resistance, it is preferable to avoid switching ARSI, and in cases where chemotherapy is an option, consideration must be given not to miss the opportunity to administer DTX or cabazitaxel. The usefulness of Ra-223 for bone metastasis is shown in CQ14 and General Statement (treatment of bone metastasis), and the usefulness of olaparib is shown in CQ4.

As mentioned in CQ11, hormone therapy combined with ARSI or DTX is expected to become a mainstream treatment for mCSPC. An important issue for discussion will be which drug to use when mCSPC progresses to CRPC. Although this is mentioned in CQ13, there is as yet insufficient evidence to draw a conclusion, and it remains a topic for future discussion.

Treatment of bone metastasis

Bone-modifying agents (BMAs) are known to significantly inhibit the onset of skeletal-related events accompanying bone metastasis and are grade B recommended in the "Japanese Clinical Practice Guidelines for Prostate Cancer 2016" for CRPC with bone metastasis. On the other hand, there is much debate regarding CSPC, and the recommendation is grade C2. The effectiveness of BMA in all survival rates and progression-free survival rates has not been proven in either CRPC or CSPC.

Nuclear medicine therapy using Ra-223 has been shown to improve the overall survival rate in CRPC patients with bone metastases. For combination therapy with ARSI, please refer to CQ14.

Palliative care

For information on drug therapy for pain relief from bone metastases, please refer to the "Clinical Guidelines for Cancer Pain Management 2020 Edition," 3rd Edition. External beam radiation therapy aimed at relieving pain from bone metastasis is a useful method. Single-session irradiation has a high rate of retreatment, and multiple-session irradiation is recommended when possible.

For cases of bone metastasis with spinal cord compression symptoms, the consensus is to use steroids, but whether or not to perform surgery should be decided considering prognosis and paralysis.

Palliative radiation therapy and/or arterial embolization for hematuria are highly effective treatments that should be considered if the condition does not improve with conservative treatment. Hyperbaric oxygen therapy should also be considered for radiation cystitis after curative radiation therapy for prostate cancer.

Recently, the importance of advance care planning has been emphasized, and end-of-life medical care involving continuous discussion regarding future treatment and care among the patient, family, surrogate decision-makers, and healthcare practitioners is necessary.

EXTERNAL EVALUATION AND PUBLIC COMMENT

These updated guidelines were evaluated by three external evaluation groups. The first was carried out by an External Evaluation Committee (doctors of urology) set up by the Japanese Urological Association, which was joined by directors of the Japanese Urological Association and patient representative who provided a clinical perspective. The second was an external evaluation by the Japanese Society for Radiation Oncology. The third was a prepublication evaluation of treatment guidelines conducted by Minds using AGREE II, focusing mainly on development methodology.

In addition, public comments were solicited using the website of the Japanese Urological Association.

CONCLUSIONS

This article is an English translation of the Clinical Practice Guidelines for Prostate Cancer (4th Edition) published in October 2023. Two new attempts have been made in this revision. The first is the incorporation of SR methods in the preparation of the report. This was our first attempt and took about 3 years to complete. We hope that the experience gained in this project will be utilized in future guideline development. The second is that patient representatives joined the revision committee and pointed out many points that we would not have noticed from the perspective of physicians alone. We sincerely hope that this guideline will be useful in daily clinical practice for all medical professionals involved in prostate cancer.

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Cooperation members of SR and General Statements are as follow: Rihito Aizawa: Department of Radiation Oncology Image-Applied Therapy, Graduate School of Medicine, Kyoto University; Koichiro Akakura: JCHO Mishima General Hospital; Hirotaka Akita: Department of Diagnostic Radiology, Keio University School of Medicine; Hiromi Edo: Department of Radiology, National Defense Medical College; Naohiro Fujimoto: Department of Urology, School of Medicine, University of Occupational and Environmental Health; Atsuko Fujihara: Department of Urology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine; Takashi Fukagai: Department of Urology Showa University School of Medicine; Tomoharu Fukumori: Department of Urology, Tokushima Municipal Hospital; Junya Furukawa: Department of Urology, Tokushima University Graduate School of Biomedical Sciences; Tomoaki Hakariya: Division of Nephro-Urology, Nagasaki University Graduate School of Biomedical Sciences; Kohei Hashimoto: Department of Urology, Sapporo Medical University School of Medicine; Shingo Hatakeyama: Department of Urology, Hirosaki University Graduate School of Medicine; Koji Hatano: Departments of Urology, Osaka University Graduate School of Medicine; Tsukasa Igawa: Department of Urology, Kurume University School of Medicine; Junichi Inokuchi: Department of Urology, Graduate School of Medicine, University of the Ryukyus; Kazuto Ito: Department of Urology, Kurosawa Hospital; Yasuhiro Kaiho: Division of Urology, Faculty of Medicine Tohoku Medical and Pharmaceutical University; Toshiyuki Kamoto: Department of Urology, Faculty of Medicine, Miyazaki University Hospital; Manabu Kato: Department of Urology Aichi Cancer Center; Masashi Kato: Department of Urology, Nagoya University; Takuma Kato: Department of Urology, Faculty of Medicine, Kagawa University; Takashi Kawahara: Department of Urology and Renal Transplantation Yokohama City University Medical Center; Satoru Kawakami: Department of Urology, Saitama Medical Center, Saitama Medical University; Yoshihide Kawasaki: Department of Urology, Tohoku University Graduate School of Medicine; Takahiro Kimura: Department of Urology, The Jikei University School of Medicine; Takashi Kobayashi: Department of Urology, Graduate School of Medicine, Kyoto University; Kenta Konishi: Department of Radiation Oncology Hamamatsu University School of Medicine; Takeo Kosaka: Department of Urology, Keio University School of Medicine; Toshiya Maebayashi: Department of Radiology, Nihon University School of Medicine; Hiroaki Matsumoto: Yamaguchi Prefectural Grand Medical Center; Ryuji Matsumoto: Department of Urology, Hokkaido University Graduate School of Medicine; Yoh Matsuoka: Department of Urology, Saitama Cancer Center; Koji Mitsuzuka: Japan Community Health Care Organization Sendai Hospital; Takefumi Miura: Secomedic Hospital; Jun Miyazaki: Department of Urology, School of Medicine, International University of Health and Welfare; Yasuhide Miyoshi: Department of Urology, Kanagawa Prefectural Ashigarakami Hospital; Shuichi Morizane: Division of Urology, Department of Surgery, Faculty of Medicine, Tottori University; Atsushi Nakamoto: Department of Diagnostic and Interventional Radiology, Osaka University Graduate School of Medicine; Katsumasa Nakamura: Department of Radiation Oncology, Hamamatsu University School of Medicine; Shintaro Narita: Department of Urology, Akita University Graduate School of Medicine; Koji Okihara: Maizuru Kyousai Hospital, Takashi Saika: Department of Urology, Ehime University Graduate School of Medicine; Shinichi Sakamoto: Department of Urology, Chiba University Graduate School of Medicine; Takefumi Satoh: Satoh Takefumi Prostate Clinic; Yoshitaka Sekine: Department of Urology, Gunma University Graduate School of Medicine; Shosei Shimizu: Department of Radiation Oncology and Proton Medical Research Centre, University of Tsukuba; Toshitaka Shin: Department of Urology, Oita University Faculty of Medicine; Masaki Shiota: Department of Urology, Graduate School of Medical Sciences, Kyushu University; Ryoichi Shiroki: Department of Urology, Fujita Health University School of Medicine; Sunao Shoji: Department of Urology, Tokai University School of Medicine; Toru Sugihara: Department of Urology, Jichi Medical University; Motofumi Suzuki: Department of Urology, The Kikkoman General Hospital; Hiroyoshi Suzuki: Department of Urology, Toho University Sakura Medical Center; Satoru Takahashi: Imaging Research Center, Takatsuki General Hospital; Hiroyuki Takahashi: Department of Pathology, The Jikei University School of Medicine; Mitsuru Takeuchi: Department of Radiology, Radiolonet Tokai; Naoki Terada: Department of Urology, Faculty of Medical Sciences, University of Fukui; Yoichiro Tohi: Department of Urology, Faculty of Medicine, Kagawa University; Toyonori Tsuzuki: Department of Surgical Pathology, Aichi Medical University; Yoshiko Ueno: Department of Radiology, Kobe University Graduate School of Medicine; Masatoshi Watanabe: Department of Oncologic Pathology, Graduate School of Medicine, Mie University; Hideo Yasunaga: Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo; Akira Yokomizo: Department of Urology, Harasanshin Hospital; Atsunori Yorozu: Department of Radiation Oncology, National Hospital Organization Tokyo Medical Center; and Yasuo Yoshioka: Radiation Oncology Department, Cancer Institute Hospital, Japanese Foundation for Cancer Research.

Cooperation members of SR support group consisting of public health and medical statisticians are as follows: Hirofumi Ohnishi: Department of Public Health, Sapporo Medical University School of Medicine; Masayuki Koyama: Department of Public Health, Sapporo Medical University School of Medicine; Nobuaki Himuro: Department of Public Health, Sapporo Medical University School of Medicine; Keiko Fujino: Department of Urology, Sapporo Medical University School of Medicine; and Takashi Yoshioka: Department of Preventive Medicine and Public Health, Keio University School of Medicine.

Members of the Evaluation Committee of JUA: Naoya Masumori: Department of Urology, Sapporo Medical University School of Medicine; Akira Miyajima: Komazawa Urology Clinic; Hiroaki Shiina: Department of Urology, Shimane

University School of Medicine, Guideline Committee of the Japanese Society for Radiation Oncology; and Hiroshi Yasue: Patient Representative.

AUTHOR CONTRIBUTIONS

Yasuo Kohjimoto: Conceptualization; data curation; methodology; validation; supervision; writing – review and editing; project administration. **Hiroji Uemura:** Conceptualization; methodology; investigation; validation; formal analysis; writing – original draft. **Masahiro Yoshida:** Conceptualization; methodology; supervision. **Shiro Hinotsu:** Methodology; conceptualization; supervision. **Satoru Takahashi:** Formal analysis. **Tsutomu Takeuchi:** Formal analysis. **Kazuhiro Suzuki:** Investigation; writing – original draft; formal analysis. **Hiroshi Shinmoto:** Investigation; writing – original draft; formal analysis. **Tsutomu Tamada:** Investigation; writing – original draft; formal analysis. **Takahiro Inoue:** Investigation; formal analysis; writing – original draft. **Mikio Sugimoto:** Investigation; formal analysis; writing – original draft. **Atsushi Takenaka:** Investigation; formal analysis; writing – original draft. **Tomonori Habuchi:** Investigation; formal analysis; writing – original draft. **Hitoshi Ishikawa:** Investigation; formal analysis; writing – original draft. **Takashi Mizowaki:** Investigation; formal analysis; writing – original draft. **Shiro Saito:** Investigation; formal analysis; writing – original draft. **Hideaki Miyake:** Investigation; formal analysis; writing – original draft. **Nobuaki Matsubara:** Investigation; formal analysis; writing – original draft. **Norio Nonomura:** Investigation; formal analysis; writing – original draft. **Hideki Sakai:** Investigation; formal analysis; writing – original draft. **Akihiro Ito:** Investigation; formal analysis; writing – original draft. **Osamu Ukimura:** Investigation; formal analysis; writing – original draft. **Hideyasu Matsuyama:** Investigation; formal analysis; writing – original draft. **Isao Hara:** Conceptualization; methodology; data curation; formal analysis; supervision; funding acquisition; project administration; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

The Japanese Association of Medical Sciences (JAMS) COI management guidance on eligibility criteria for clinical practice guideline formulation 2017 was used to monitor each member's COI. COI declarations by all members involved in the development of these guidelines have been carefully examined by COI committee of JUA and published on the website (https://www.urol.or.jp/lib/files/other/guideline/23_prostatic_cancer_coi.pdf). When voting on the recommendation, the committee members with COI regarding the content of the CQ were to abstain from voting.

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