National Kidney and Transplant Institute

Philippine Clinical Practice Guideline for the Diagnosis and Management of Prostate Cancer

2021

Department of Health

DISCLAIMER

This clinical practice guideline (CPG) is intended to be used by specialists and general practitioners who are primary care providers. Although adherence to this guideline is encouraged by the Department of Health (DOH), it should not restrict the clinicians in using their clinical judgment and considering patient's values, needs, and preferences while handling individual cases. Clinicians and relevant stakeholders must always exercise sound clinical decision-making as the individual patient's history, current physical status, and their responses to treatment may vary.

Payors and policymakers, including hospital administrators and employers, can also utilize this CPG, but nonconformance to this document should not be the sole basis for granting or denying financial assistance or insurance claims. Recommendations from this CPG should not be treated as strict rules to base legal action upon.

Developers of this CPG are aware of its limitations. Evidence summaries are based on the best available scientific evidence at the time of its formulation. As such, certain aspects of the interventions or diagnostic tests may not be completely addressed by the included studies.

This CPG is not intended to cover the entirety of the management of prostate cancer. It provides recommendations on interventions where variability in clinical practice and some controversies in decision-making exist.

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EXECUTIVE SUMMARY

In January 2021, the Disease Prevention and Control Bureau - Cancer Control Division of the Department of Health, under the National Integrated Cancer Control Program, sub-allocated funds to the National Kidney and Transplant Institute (NKTI) to support the development of Clinical Practice Guideline for Prostate Cancer.

The Executive Director of NKTI ordered the creation of a Steering Committee (SC) for the Prostate Cancer CPG Task Force. The SC formulated research questions based on the 10 most common situations in the diagnosis or treatment of prostate cancer where there were uncertainties or variance in the approach. The SC then recruited expert consultants, technical coordinators and evidence review experts (EREs) which composed the Technical Working Group (TWG) of the Task Force. The SC invited representatives from specialty societies and interest groups on prostate cancer to comprise the multi-sectoral Consensus Panel (CP).

The Philippine Clinical Practice Guideline for the Diagnosis and Management of Prostate Cancer aims to provide evidence-based recommendations (Table 1) for the diagnosis and management of prostate cancer. This document is intended to be used by oncologists, other specialists, general physicians, allied health professionals, academicians, policy-makers and other sectors involved in the care of patients with prostate cancer. The recommendations shown below were based on the best available evidence and formulated through the "Grading of Recommendations, Assessment, Development and Evaluation" or GRADE approach. These recommendations shall be updated as new evidence, technology, or patient or healthcare provider preferences arise.

Table 1. Summary of Recommendations

	Recommendations	Certainty of Evidence	Strength of Recommendation
1	Among patients with localized intermediate- or high-risk prostate cancer, we recommend the use of either radiation therapy or radical prostatectomy as first-line therapy.	Low	Strong
2	Among patients with newly diagnosed intermediate- or high-risk localized prostate cancer treated with definitive radiotherapy, we recommend the use of neoadjuvant or adjuvant androgen deprivation therapy over observation.	Low	Strong
3	Among patients with localized prostate cancer who have residual disease after radical prostatectomy, we recommend close monitoring and salvage radiation therapy in the event of clinical or biochemical progression.	Very low	Strong

4	Among patients with locally advanced prostate cancer with extra-prostatic extension but no lymph node involvement, we recommend to give androgen deprivation therapy and radiotherapy over androgen deprivation therapy alone.	Low	Strong
5	Among patients with newly-diagnosed prostate cancer and M1 metastasis, either asymptomatic with high or very high-risk features of disease, or symptomatic regardless of risk, a. we suggest the addition of docetaxel alone or abiraterone alone. b. we suggest against adding EBRT to ADT.	Very low	Weak
6	Among patients with castration-sensitive metastatic prostate cancer with low metastatic burden (< 5 bone metastases), we suggest androgen deprivation therapy and radiotherapy to the primary tumor.	Very low	Weak
7	Among patients with metastatic castrate-resistant prostate cancer, we suggest systemic chemotherapy with or without androgen deprivation therapy. However, we suggest resuming androgen deprivation therapy if serum testosterone increases above 50 ng/dL.	Very low	Weak
8	Among prostate cancer patients with bone metastases, we suggest against the addition of a bone-modifying agent to radiotherapy to reduce skeletal-related adverse events.	Very low	Weak
9	Among patients with a single elevated prostate-specific antigen and normal digital rectal exam, we suggest watchful waiting with risk factor assessment and serial PSA monitoring over doing a prostate biopsy.	Very low	Weak
10	Among patients with biochemical recurrence of prostate cancer after local therapy, there is insufficient evidence to suggest the use of PSMA PET/CT over conventional imaging.	Very low	None

LIST OF ABBREVIATIONS

3DCRT	3D conformal radiation therapy
ADT	Androgen deprivation therapy
ASTRO	American Society for Radiation Oncology
AUA	American Urological Association
BCR	Biochemical recurrent
CCO	Cancer Care Ontario
CRPC	Castrate-resistant prostate cancer
c/rPFS	Clinical/radiographic progression-free survival
CoE	Certainty of evidence
CoI	Conflicts of Interest
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
CPG	Clinical Practice Guidelines
DOH	Department of Health
DRE	Digital rectal examination
EAU	European Association of Urology
EANM	European Association of Nuclear Medicine
EBRT	External beam radiotherapy
ESMO	European Society of Medical Oncology
ESRO	European Society for Radiotherapy and Oncology
ESUR	European Society of Urogenital Radiology
EORTC QLQ	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
FACT-P	Functional Assessment of Cancer Therapy-Prostate Questionnaire
IMRT	Intensity-modulated radiation therapy
ISGO	International Society of Geriatric Oncology
LHRH	Luteinizing hormone-releasing hormone
MD	Mean difference
NCCN	National Comprehensive Cancer Network
PCSS	Prostate Cancer Symptom Scale
PSA	Prostate-specific antigen
PSMO	Philippine Society of Medical Oncology
QALY	Quality Adjusted Life Years
QOL	Quality of life
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
RCT	Randomized controlled trial
SUO	Society of Urologic Oncology

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CHAPTER 1. BACKGROUND

Prostate cancer is the 5th most commonly diagnosed cancer in the Philippines [1]. The Global Cancer Network Observatory or GLOBOCAN 2020 data show that in the Philippines, an estimated 8242 males are diagnosed with this dreaded disease annually. It is an emerging health concern for Filipino men.

In the 2020 NKTI Hospital Cancer Registry, Blood Dyscrasia, Kidney Cancer, and Prostate and Other Male Genital Cancers made up 23%, 14% and 12% of their total 1,346 registrants, respectively. This is in contrast to 5%, 3% and 5% of the 9,880 registrants in the 2020 CARE PH central database for the same three cancer types [2].

The Department of Health recognizes the National Kidney and Transplant Institute as the premier hospital for the diagnosis and treatment of kidney and urologic diseases, including kidney and urologic malignancies. The NKTI, in 2020, was therefore designated by the DOH as an Advanced Comprehensive Specialty Cancer Center for Kidney and Urologic Malignancies [3].

The National Integrated Cancer Control Act of 2019 prioritizes high quality of cancer care in the community and in specialty hospitals to ensure the maximum possible cure rates and the best quality of life for patients diagnosed with cancer [4]. The National Integrated Cancer Control Strategic Plan likewise emphasizes robust information systems and technologies and cutting-edge research, including the creation of CPGs as one of its pillars in its strategic plan framework for 2021-2030 [5]. The DOH has designated some of its major hospitals, including Rizal Medical Center, East Avenue Medical Center, Southern Philippines Medical Center, and NKTI to receive funding for the administration and creation of CPGs for specific common cancers in the Philippines.

The survival rates for localized and locally advanced cancers are excellent when diagnosed early and treated properly, which is why it is critical to standardize diagnostic and treatment practice across all levels of cancer care. Creating guidelines tailored to our local setting will serve as a reference point from which the DOH and Philhealth can create effective policies for prostate cancer management and programs for prostate cancer awareness and screening. Physicians will then be able to adequately and equitably treat patients with prostate cancer.

References:

[1] Global Cancer Observatory (2021, March) Philippine Population Fact Sheets. https://gco.iarc.fr/today/data/factsheets/populations/608-philippines-fact-sheets.pdf

[2] 2020 CARE PH Annual Report

[3] DOH Department Order 2021-0001 Designation of Selected DOH Hospitals as Specialty Centers for Brain and Spine Care, Burn Care, Cancer Care, Cardiovascular Care, Dermatology Care, Eye Care, Geriatric Care, Infectious Disease and Tropical Medicine, Lung Care, Mental health, Neonatal Care, Orthopedic Care, Physical Rehabilitation Medicine, Renal Care and Kidney Transplant, Toxicology, and Trauma Care

[4] Implementing Rules and Regulations (IRR) of the Republic Act No. 11215, Otherwise known as the National Integrated Cancer Control Act

[5] The National Integrated Cancer Control Strategic Plan 2021-2030 (DRAFT)

CHAPTER 2. GUIDELINE DEVELOPMENT METHODS

Organization of the Process

The National Kidney and Transplant Institute (NKTI) identified the members of the Steering Committee (SC) who supervised the formulation of the CPG. The SC formed two other working groups, the Technical Working Group (TWG) and the Consensus Panel. The TWG was composed of evidence review experts who took charge of literature search, evidence review, and synthesis. The Consensus Panel (CP) was composed of nine representatives from different sectors of society, including health practitioners and patient advocates. They were nominated and authorized by their respective specialty groups to represent the voice of their organization in formulating the final recommendations. The Steering Committee identified the members of the Consensus Panel according to their knowledge, expertise in the field, and absence of conflicts of interest (COI).

The "Grading of Recommendations, Assessment, Development, and Evaluation or GRADE Approach" and the "2018 DOH Manual for Clinical Practice Guideline Development" were used as guides for the entire development process. The Department of Health provided funding for the creation of this CPG, however, it did not have any other influence in the CPG development process.

Creation of the Evidence Base

The SC formulated 10 research questions (Table 2) to address relevant issues on the diagnosis and treatment of prostate cancer in the country. The research questions identified by the SC were finalized after due consultation with the Consensus Panel.

Table 2. List of Research Questions

1	Among patients with localized prostate cancer, should we do radiation (external beam radiation therapy or brachytherapy) or radical prostatectomy as first-line therapy to improve overall survival, progression-free survival, and quality of life?
2	Among patients with newly-diagnosed localized prostate cancer treated with definitive radiotherapy, should we use neoadjuvant or adjuvant androgen deprivation therapy versus observation to improve overall survival, progression-free survival, and quality of life?
3	Among patients with localized prostate cancer who have undergone radical prostatectomy but with residual disease, should we give radiation therapy post-operatively versus observation to improve overall survival, progression-free survival, and quality of life?
4	Among patients with locally advanced prostate cancer with extra-prostatic extension but no lymph node involvement, should we use androgen deprivation therapy and radiotherapy versus androgen deprivation therapy alone to improve overall survival, progression-free survival, and quality of life?
5	Among patients with newly-diagnosed prostate cancer and M1 metastasis, either asymptomatic with high or very high-risk features of disease, or symptomatic regardless of risk, should we give androgen

	deprivation therapy and external beam radiotherapy or docetaxel and/or abiraterone vs. androgen deprivation therapy alone to improve overall survival, progression-free survival, and quality of life?
6	Among patients with castration-sensitive metastatic prostate cancer with low metastatic burden, should we give androgen deprivation therapy and radiotherapy to the primary tumor versus androgen deprivation therapy alone to improve overall survival, progression-free survival, prostate cancer-specific survival, and quality of life?
7	Among patients with metastatic castrate-resistant prostate cancer, should we give systemic therapy with androgen deprivation therapy versus systemic therapy alone (chemotherapy or non-chemotherapy) to improve overall survival, progression-free survival, and quality of life?
8	Among prostate cancer patients with bone metastases, should we add bone modifying agents to radiotherapy or use radiotherapy alone to improve overall survival and reduce skeletal-related events?
9	Among patients with elevated prostate-specific antigen (PSA) and normal digital rectal exam with no other known cause for elevated PSA, should we do prostate biopsy versus watchful waiting to improve overall survival, progression-free survival, and quality of life?
10	Among patients with biochemical recurrence of prostate cancer after local therapy, should we do PSMA PET-CT (plain or with contrast) versus conventional imaging (bone scan and whole abdomen with contrast with or without CT scan of the chest) to improve overall survival, progression-free survival, and quality of life?

For this CPG, the de novo approach in the creation of the evidence base was utilized. A systematic search of local and international electronic databases (i.e.,MEDLINE, CENTRAL, Google Scholar, HERDIN, and clinicaltrials.gov) was conducted by the Evidence Review Experts (ERE). For each research question, the scope (inclusion and exclusion criteria) of the literature search was dictated by the population, intervention, comparator, outcomes, and methodology (PICOM). For therapeutic interventions, the reviewers looked for direct evidence from randomized controlled trials (RCT), systematic reviews (SR), and/or meta-analyses. In their absence, quasi-randomized and observational studies were assessed for possible inclusion. For diagnostic interventions, observational studies that reported sensitivity, specificity, and other diagnostic accuracy estimates and RCT and SR reporting clinical outcomes of benefit or harm of these interventions and resulting treatment were sought.

Two EREs independently appraised the methodological quality of each individual study using the Cochrane Risk of Bias Tool. Studies with similar PICO were pooled and the effect estimates were determined using RevMan 5.0. The certainty of the evidence (CoE) for each outcome of interest was assessed using GRADEPro, which considers the risk of bias and presence or absence of any indirectness, imprecision, inconsistency, and other considerations (i.e., publication bias). The overall certainty of evidence was based on the lowest certainty rating of the top 7 critical and important outcomes. The rating of importance of outcomes into critical, important, or relevant was decided on by the multi-sectoral consensus panel.

The appraisal of included studies in the reviews for each research question and the synthesis of their effect estimates for critical and important outcomes are presented in an evidence summary. The balance of benefit and risks became the basis for the draft recommendations. The evidence summaries were compiled into the Evidence Base and submitted prior the consensus panel meetings to guide in the decision-making process of the multi-sectoral consensus panel.

Formulation of Recommendations

The CP members reviewed the evidence and the draft recommendation formulated by the TWG. Through an online survey, they determined the relative importance of all outcomes for each research question, in clinical decision-making. Each outcome was scored from a scale of 1-9. Outcomes rated 7-9 were considered as critical outcomes; 4-6 were important but not critical outcomes; and, those outcomes that were rated 1-3 are of limited importance.

There were four remote or virtual en banc meetings to discuss key points about the evidence and exchange opinions, preferences, and clinical experiences. Once all issues were clarified, the members of the CP voted on the recommendation statement and the strength of recommendation. The grading of the strength of recommendation was based on the (1) overall quality of the evidence; (2) trade-offs between benefits and harms; (3) values and preferences of patients; (4) resource implications; and, (5) impact on equity.

A consensus vote was an agreement of 70% among the panelists. When consensus was not reached, the panel members discussed the reasons in support of their votes. Voting was repeated up to three times until a consensus was reached.

Managing Conflicts of Interest

All members (i.e., SC, TWG, CP) involved in the development of this CPG declared all potential conflicts of interest through a standard Declaration of Conflict of Interest Form. The SC reviewed the accomplished CoI forms of each member of the task force and did not find any significant CoI.

CHAPTER 3. RECOMMENDATIONS AND EVIDENCE TO DECISION ISSUES

The recommendations and evidence summaries are briefly outlined in the following pages. More details of the evidence can be found in a supplementary document (Evidence Base).

Radiation therapy versus radical prostatectomy as first-line therapy for localized prostate cancer

Recommendation

1. Among patients with localized intermediate- or high-risk prostate cancer, we recommend the use of either radiation therapy or radical prostatectomy as first-line therapy.
Certainty of Evidence: Low
Strength of Recommendation: Strong

Prostate cancer is localized when it is confined within the prostate. This is also called early or stage T1 or T2 prostate cancer [1]. It can be stratified into low, intermediate, or high-risk disease based on the risk of progression and recurrence after definitive therapy. Low-risk disease has been shown to have a cancer-specific survival of 99% when treated. However, patients with high-risk prostate cancer present with lower survival rates [1,2].

Evidence to Decision

Benefit and Harm

Eight randomized controlled trials (RCTs, n=1,907 patients) [3-10] compared the use of radical prostatectomy and definitive radiotherapy (RT) [i.e., external beam RT (EBRT) or brachytherapy] among patients with localized prostate cancer. The analysis of oncologic outcomes [3-9] showed inconclusive difference in effect estimates between the two interventions (Table 5). These outcomes were biochemical recurrence at five (RR: 0.63; 95% CI 0.32, 1.23) and ten years (RR: 0.84; 95% CI 0.42, 1.65); clinical recurrence at five (RR: 0.45; 95% CI 0.10, 1.90) and ten years (RR: 0.74; 95% CI 0.36, 1.51); distant metastases (RR: 0.80; 95% CI 0.38, 1.67); death from prostate cancer at five (RR: 0.58; 95% CI 0.11, 2.99) and ten years (RR: 1.01; 95% CI 0.41, 2.47); and, death from any cause at five (RR: 0.53; 95% CI 0.22, 1.30) and ten years (RR: 0.97; 95% CI 0.73, 1.28).

Urinary, bowel, and sexual function scores were measured in the four studies [3,4,6,8] which reported quality of life (QOL) at 6, 12, and 24 months. Radical prostatectomy resulted in more events of urinary symptoms (RR: 2.90; 95% CI 1.60, 5.26) and erectile dysfunction (RR: 1.39; 95% CI 1.18, 1.63) than radiotherapy but lower incidence of fecal incontinence, loose or bloody stools (RR: 0.42; 95% CI 0.20, 0.91). Based on minimum clinically important difference of + 7 points, there was no significant difference in global quality of

life (EORTC QLQ-C30) between the two interventions at 6 (MD: 0.07; 95% CI: -4.05, 4.20) and 12 months (MD: -0.74; 95% CI: -8.02, 6.54).

The overall CoE for all outcomes was moderate due to imprecision. Biochemical recurrence at five years and quality of life were further downgraded due to selection bias and clinical recurrence at five and ten years due to inconsistency arising from differences in the disease risk category of the participants.

Other Considerations

Cost

There was no cost-effectiveness study that compared the two interventions. Both were deemed to entail significant cost but radiotherapy was considered of lower direct cost than radical prostatectomy. Table 3 below shows the estimated cost of radical prostatectomy and laparoscopic approach. Table 4 on the other hand shows the estimated cost of different radiotherapy modalities. These costs were gathered on September 2021 from an informal survey of practicing clinicians in tertiary hospitals and practicing clinicians and limited to the direct medical cost of the procedures.

Table 3. Cost of radical prostatectomy and laparoscopic prostatectomy

Intervention	Cost
Radical prostatectomy	Php 40,000.00- 180,000.00
Laparoscopic prostatectomy	Php 200,000.000

Table 4. Cost of different radiotherapy modalities for 35 sessions

Modality	Cost per session	Cost for 35 sessions
Treatment planning (any RT modality)		Php 15,000.00- Php 20,000.00
3D Conformal RT	Php 1,000.00 to Php 1,428.57	Php 35,000.00 to Php 50,000.00
Cobalt radiotherapy (with Philhealth coverage or special discounts)	Php 2,000.00	Php 70,000.00
Intensity- modulated RT (IMRT) (with Philhealth coverage or special discounts)	Php 3,071.00	Php 107,000.00
IMRT (without Philhealth coverage or special discounts)	Php 6,571.00	Php 230,000.00
Linear accelerator (with Philhealth coverage or special discounts)	Php 3,000.00	Php 105,000.00
Hypofractionated RT (with Philhealth coverage or special discounts)	Php 3,000.00	Php 105,000.00
Hypofractionated RT (without Philhealth coverage or special discounts)	Php 8,000.00	Php 280,000.00

Other Guidelines

National Comprehensive Cancer Network (NCCN) recommended radical prostatectomy or radiotherapy (i.e., EBRT, brachytherapy) as treatment options for localized prostate cancer [11].

The American Urological Association (AUA), American Society for Radiation Oncology (ASTRO), Society of Urologic Oncology (SUO) advocated for shared decision-making that considers the patient's risk category, patient values and preferences, life expectancy, symptoms, functional status, and potential for salvage treatment. Active surveillance is preferred by AUA and ASTRO for most patients with low-risk disease or asymptomatic patients with high-risk disease and limited life expectancy. Definitive treatment is considered only in the minority who have a high probability of progression. Prostatectomy or RT+ADT are considered standard options for intermediate- and high-risk patients [12].

The European Association of Urology (EAU), European Association of Nuclear Medicine (EANM), European Society for Radiotherapy and Oncology, European Society of Urogenital Radiology, International Society of Geriatric Oncology guidelines on screening, diagnosis, and local treatment of clinically localized prostate cancer echo these recommendations [13].

Consensus Issues

Despite the low CoE, the panel gave a strong recommendation for either radiotherapy or radical prostatectomy because for patients with life expectancy >10 years, the objective is to go for a cure, which is possible with either of the two interventions. If doctors do not actively intervene, the cancer will surely advance.

RT can be administered as an internal beam (brachytherapy) or as an external beam (EBRT). In local practice, brachytherapy is used for very low- and low-risk patients. For intermediate- and high-risk patients, EBRT alone or a combination of EBRT and brachytherapy is used. If combined with brachytherapy, the dose of EBRT may possibly be reduced. EBRT has many types, namely: 3-dimensional conformal (3DCRT), intensity-modulated (IMRT), image-guided (IGRT), stereotactic (SRT), stereotactic body radiation therapy (SBRT), and proton therapy. The newer types of EBRT modality, like IMRT, are associated with fewer occurrences of adverse events and better treatment compliance but higher direct treatment cost.

As mentioned in international guidelines, it is imperative to stratify risk after diagnosis to guide treatment planning. Active treatment with surgery or RT was specifically recommended for patients with more aggressive or intermediate- to high-risk tumors. For low-risk disease, active surveillance is the common local practice.

Patient characteristics (i.e. life expectancy, age, existing comorbidities, capacity to handle adverse effects of treatment, overall patient condition), personal preference, risk of disease progression, and possible adverse effects of treatment should be discussed between the physician and the patient and weighed when choosing between RT and radical prostatectomy.

The evidence showed similar benefits from both interventions, and these treatments were perceived to be acceptable and likely feasible. However, delivering these health technologies to patients nationwide may be a challenge to the government. Stating the recommendation as a strong one may push the health system to provide for these needed treatments. Direct non-medical cost, indirect cost, and the social perspectives of care need to be studied to fully determine the cost implications on a national scale.

Table 5. Summary of outcomes from Key Question 1

OUTCOME	NO. OF INCLUDED RCTs	n	EFFECT MEASUREMENT [95%CI]	INTERPRETATION	
Biochemical Recurrence					
at 5 years	3	366	RR: 0.63; 95% CI 0.32,1.23	Inconclusive	
at 10 years	1	95	RR: 0.84; 95% CI 0.42,1.65	Inconclusive	M
Clinical Recurrence					
at 5 years	2	192	RR: 0.45; 95% CI 0.10,1.90	Inconclusive	V
at 10 years	2	1,193	RR: 0.74; 95% CI 0.36,1.51	Inconclusive	
Distant metastases					
at 10 years	1	1,098	RR: 0.80; 95% CI 0.38,1.67	Inconclusive	M
Death from prostate cancer					
at 5 years	3	1,282	RR: 0.58; 95% CI 0.11,2.99	Inconclusive	
at 10 years	3	1,282	RR: 1.01; 95% CI 0.41,2.47	Inconclusive	M
Deaths from any cause					
at 5 years	1	95	RR: 0.53; 95% CI 0.22,1.30	Inconclusive	M
at 10 years	3	1,282	RR: 0.97; 95% CI 0.73,1.28	Inconclusive	M
Quality of Life					
Urinary Symptoms	1	950	RR 2.90; 95% CI 1.60,5.26	Significant harm with RP	
Erectile Dysfunction	1	703	RR 1.39; 95% CI 1.18,1.63	Significant harm with RP	
Bowel symptoms	1	723	RR 0.42; 95% CI 0.20,0.91	Significant harm with RT	

CoE: Certainty of Evidence
CI: confidence interval
RCT: randomized controlled trial
RR: risk ratio
RT: radiotherapy

Androgen deprivation therapy for newly-diagnosed localized prostate cancer given radiotherapy

Recommendation

2. Among patients with newly-diagnosed intermediate- or high-risk localized prostate cancer treated with definitive radiotherapy, we recommend the use of neoadjuvant or adjuvant androgen deprivation therapy over observation.
Certainty of Evidence: Low
Strength of Recommendation: Strong

Androgen deprivation therapy (ADT) is used as additional treatment for some patients with localized prostate cancer already given definitive radiotherapy. ADT is either through surgical (orchiectomy) or medical castration. Examples of androgen suppressants include luteinizing hormone releasing hormone (LHRH) agonists or antagonists, or androgen-receptor blockers. Oral anti-androgens can be nonsteroidal: bicalutamide, flutamide, nilutamide, or steroidal: cyproterone acetate. They inhibit binding of dihydrotestosterone (DHT) and testosterone to the receptor but serum testosterone levels are not affected or reduced. In contrast, LHRH agonists (i.e.,leuprolide acetate, triptorelin pamoate, goserelin acetate, histrelin acetate) and antagonists lower circulating testosterone. ADT can be given prior to definitive therapy (neoadjuvant) or after the procedure (adjuvant). ADTs are usually given every 1, 3 or 6 months depending on the drug, dosage, and preparation. The optimal duration of ADT is not established but data suggest that longer duration improves outcomes [14,15].

Evidence to Decision

Benefit and Harm

Seven published [16-22] reports from four clinical trials [16,18,20,21] were analyzed to evaluate the effect of neoadjuvant/adjuvant ADT versus observation. Pooled results of three RCTs (n=1,148) [16,18,20] showed statistically significant benefit with the use of ADT in improving 5-year progression-free survival (RR: 0.49; 95% CI 0.27, 0.88; I^2=91%), 10-year progression-free survival (RR: 0.50; 95% CI 0.33, 0.77; I^2=74%), and 10-year overall survival (RR: 0.75; 95% CI 0.62, 0.92; ; I^2=76%) (Table 7). Subgroup analysis was only done for the timing of ADT administration and not for cancer risk groups since risk stratification was not available for all studies. Both neoadjuvant and adjuvant administration of ADT was able to improve 5- and 10-year progression-free survival. The 10-year overall survival data favored the adjuvant administration of ADT (RR RR: 0.70; 95% CI 0.57, 0.87), while neoadjuvant administration was as good as or better than observation (RR: 0.77; 95% CI 0.58, 1.03; I^2=84%).

With regards adverse effects of treatment, ADT is as good as or worse than observation in terms of urinary adverse events (RR: 1.17; 95% CI 0.97, 1.42; I^2=0%) but as good as or better than observation for gastrointestinal events (RR: 0.92; 95% CI 0.81, 1.03; I^2=91%). Impotence is more likely to occur with the use of ADT (RR: 1.21; 95% CI 1.03, 1.44; I^2=0%) [20,22].

The CoE on survival outcomes was rated moderate because of substantial heterogeneity attributed to variations in ADT administration (drugs used, timing, and duration of management). For adverse event outcomes, CoE was low because of lack of blinding and imprecision.

Other Considerations

Cost

There was no local cost-effectiveness study on the use of ADT in prostate cancer. One study in the USA [23] conducted a cost-utility analysis for RT, RT and ADT, and active surveillance. It showed that gains in quality-adjusted life years (QALYs) were substantially reduced due to treatment-associated adverse events. RT and ADT (USD 127,900 per QALY) were more cost-effective than RT alone. There was no significant difference in QALYs between RT and ADT (mean QALYs 8.91; 95% CI 8.56, 9.26), active surveillance (mean QALYs 8.75; 95% CI 8.35, 9.15), and radiation (mean QALYs 8.56; 95% CI 8.19 – 8.92) [24]. The cost of locally available ADT was deemed moderately high, hence, its affordability may be a concern. Some of the costs listed below were lifted from the Drug Price Reference Index [25] while others were gathered through informal inquiry from local practitioners and institutions on September 2021. Table 6 below shows the annual treatment cost of ADT.

Table 6. Annual treatment cost 'of locally available ADTs

ADT	Annual Treatment Cost
Bicalutamide 50 mg tablet	Php 10,950.00
Bicalutamide 150 mg tablet	Php 19,102.06
Degarelix 80 mg vial for injection	Php 40,100.00
Degarelix 120 mg vial for injection	Php 57,500.00
Flutamide 250 mg tablet	Php 120,960.00-Php 140,112.00
Goserelin acetate 3.6 mg (short-term treatment for 4-6 months)	Php 16,475.20 – Php 24,712.80.
Goserelin acetate 3.6 mg (long-term treatment for 1-3 years)	Php 49,425.60 – Php 148,276.80.
Gosereline 10.8 mg depot solution in a pre-filled syringe (short-term treatment for 4-6 months)	Php 56,311.56 - Php 84,476.34
Gosereline 10.8 mg depot solution in a pre-filled syringe (long-term treatment for 1-3 years)	Php 168,934.68 - Php 506,804.04
Leuprolide 3.75 mg/2 ml (vial + syringe) (short-term treatment for 4-6 months)	Php 20,000.00 – Php 30,000.00
Leuprolide 3.75 mg/2 ml (vial + syringe) (long-term treatment for 1-3 years)	Php 60,000.00 – Php 180,000.00
Leuprolide 11.25 mg powder depot solution (vial + syringe) (short-term treatment for 4-6 months)	Php 45,276.00 - Php 67,914.00

Leuprolide 11.25 mg powder depot solution (vial + syringe) (long-term treatment for 1-3 years)	Php 135,828.00 - Php 407,484.00
Triptorelin 3.75 mg vial for injection	Php 231,408.00
Triptorelin 11.25mg vial for injection	Php 66,068.00
Triptorelin 22.5mg vial for injection	Php 25,892.00

Other Guidelines

The NCCN [26], EAU [27], and ESMO [28] recommended the addition of ADT for 4-6 months for intermediate-risk patients, and long-term (1-3 years) for high-risk patients. ADT was also considered in low-risk patients if they have lymph node metastasis.

Consensus Issues

The panel deemed it important to specify that the recommendation is specifically for intermediate to high-risk prostate cancer. The panel weighed benefit over harm with the use of neoadjuvant or adjuvant ADT. Neoadjuvant administration of ADT aids in shrinking the tumor size and may lessen the needed dose and side effects of radiation. On the other hand, adjuvant ADT suppresses the growth of cancer cells that were not eradicated by radiotherapy. The aim for these patients is still cure and this is primarily why the panel pushed for a strong recommendation.

The acceptability of the addition of ADT to RT is threatened by adverse events, especially impotence. Studies showed that the longest observed period of impotence was for five years. Locally, there is an observed high compliance rate within the first two to three years of treatment with ADT but patients tend to drop out afterwards due to adverse effects, specifically gastrointestinal and hepatic, and possibly also due to cost of treatment. Active efforts should be done to address these adverse events in order to prevent treatment drop- outs.

Table 7. Summary of outcomes for Key Question 2

OUTCOME	NO. OF INCLUDED RCTs	n	EFFECT MEASUREMENT [95%CI]	INTERPRETATION	CoE
Progression-free survival					
5 year PFS	3	1,148	RR: 0.49; 95% CI 0.27,0.88	Significant benefit with ADT+RT	Moderate
10 year PFS	3	3,466	RR: 0.50; 95% CI 0.33,0.77	Significant benefit with ADT+RT	Moderate
Overall survival					
10 years	3	2,919	RR: 0.75; 95% CI 0.62,0.92	Significant benefit with ADT+RT	Moderate
Adverse effects					
Urinary Symptoms	2	1,190	RR: 1.17; 95% CI 0.97,1.42	As good as or worse than RT alone	Low
Gastrointestinal Symptoms	2	1,200	RR: 0.92; 95% CI 0.81,1.03	As good as or better than RT alone	Low
Impotence	2	587	RR: 1.21; 95% CI 1.03,1.44	Significant harm with ADT+RT	Moderate

ADT: androgen deprivation therapy
CoE: Certainty of Evidence
CI: confidence interval
RCT: randomized controlled trial
RR: risk ratio
RT: radiotherapy

Radiotherapy versus observation for localized prostate cancer with residual disease post-prostatectomy

Recommendation

3. Among patients with localized prostate cancer who have residual disease after radical prostatectomy, we recommend close monitoring and salvage radiation therapy in the event of clinical or biochemical progression.
Certainty of Evidence: Very low
Strength of Recommendation: Strong

Radical prostatectomy allows for long-term local control and survival when prostate cancer is still localized. However, pathologic high-risk features (i.e. positive surgical margins, extra-prostatic extensions, seminal invasion) have been identified as independent predictors of biochemical relapse. The risk of failure of local treatment ranges from 10% to 50% when the cancer extends beyond the prostatic capsule or invades the seminal vesicles [29].

Evidence to Decision

Benefit and Harm

Five RCTs [30-34] compared adjuvant radiotherapy (RT) and observation among patients with localized prostate cancer who underwent radical prostatectomy. There was no significant difference between the two interventions in terms of disease-specific survival [30-32] (RR: 0.78; 95% CI 0.48, 1.26; I^2=0%), overall survival [30-34] (RR: 0.99; 95% CI 0.85, 1.16; I^2=11%), and metastases-free survival [31-34]. (RR: 0.90; 95% CI 0.73, 1.10; I^2=0%) (Table 8). Adjuvant RT reduced the risk of local recurrence [30,31] (RR: 0.42; 95% CI 0.29, 0.60; I^2=0%) and improved biochemical progression-free survival [31-34] (RR: 0.63; 95% CI 0.51, 0.78; I^2=72%) of all included subjects and of the subset of patients with positive surgical margins (RR: 0.63; 95% CI 0.53, 0.73; I^2=48%) [30,32].

The use of adjuvant RT had a higher risk of gastrointestinal (RR: 3.62; 95% CI 1.01, 13.07; I^2=75%) and genitourinary toxicities (RR: 1.65; 95% CI 1.20, 2.27; I^2=77%) [31,33]. There was no significant difference in the occurrence of erectile dysfunction [31,32] (RR: 1.02; 95% CI 0.98, 1.05; I^2=0%). One study [30] showed that patients treated with adjuvant RT who are aged 70 and above had higher risk of clinical progression [HR: 1.78; 95% CI 1.14, 2.78] and to die of any cause [HR: 2.94; 95% CI 1.75, 4.93].

The CoE for outcomes on survival and adverse events was very low for all except for local recurrence (graded as low) and biochemical progression-free survival (moderate) in patients with positive surgical margins due to issues arising from attrition bias, indirectness, inconsistency, and imprecision.

Other Considerations

Cost

There was no local cost-effectiveness study on the use of adjuvant RT for localized prostate cancer after radical prostatectomy. Cost estimates from local practice showed that adjuvant radiation administration, depending on the technique, and the treatment of its complication (Php 107,500.00-Php 230,000.00) is significantly more expensive than the cost of radical prostatectomy followed by observation (Php 40,000.00-Php 180,000.00). Refer to Tables 3 and 4 under Key Question 1 for the cost of different RT modalities and radical prostatectomy.

Other Guidelines

The AUA recommends adjuvant RT for patients who underwent radical with adverse pathologic findings (i.e., seminal vesicle invasion, positive surgical margins, and extraprostatic extension) [35]. Likewise, NCCN recommends consultation with the AUA guidelines and adjuvant RT for patients with pT3a disease, positive margin(s), or seminal invasion. They also recommend salvage radiation therapy for patients with undetectable PSA who subsequently becomes detectable on 2 measurements or a PSA that remains detectable after radical prostatectomy [36]. ESMO recommends observation with salvage RT in the presence of PSA and clinical failure [37].

Consensus Issues

The intent of treatment in this population with residual disease post-prostatectomy is to achieve cure. In local practice, adjuvant radiation therapy is not done immediately after radical prostatectomy because the surgical site must be given time to heal (six to nine months). Early administration of radiation may impair wound healing and more harm. Post-surgical patients should have undetectable PSA levels (PSA = <0.2) to indicate complete removal of the tumor. After definitive treatment, NCCN recommends monitoring every 6 months for 5 years and then annually thereafter. In the local practice, the PSA level is usually checked 4-6 weeks after surgery and then every 3 months. Patients with high risk for progression and who have detectable PSA levels should be closely monitored and informed of the need for possible future treatment. It was clarified that the type and number of sessions and radiation techniques used for adjuvant and salvage radiation therapy are the same.

Unlike in clinical trials wherein there is a highly controlled setting and a relatively good follow-up rate, in the real world, follow-up rate after prostatectomy deteriorates after a year. This may be worse among patients from disadvantaged (poor and distant) areas in the country. The importance of follow-up consultations and tests must be emphasized to patients.

Table 8. Summary of outcomes for Key Question 3

OUTCOME	NO. OF INCLUDED RCTs	n	EFFECT MEASUREMENT [95%CI]	INTERPRETATION	CoE
Disease-specific survival	3	1,588	RR: 0.78; 95% CI 0.48,1.26	Inconclusive	Very low
Overall survival	5	2,398	RR: 0.99; 95% CI 0.85,1.16	Equivalent	Very low
Metastases-free survival	4	2,013	RR: 0.90; 95% CI 0.73,1.10	Inconclusive	Very low
Local recurrence	2	1338	RR: 0.42; 95% CI 0.29,0.60	Significant benefit with adjuvant RT	Low
Biochemical progression-free survival	5	2398	RR: 0.63; 95% CI 0.51,0.78	Significant benefit with adjuvant RT	Very Low
Biochemical PFS among those with positive margins	2	852	RR: 0.63; 95% CI 0.53,0.73	Significant benefit with adjuvant RT	Moderate
Adverse Events					
Gastrointestinal Symptoms	3	1,008	RR: 3.62; 95% CI 1.01,13.07	Significant harm with adjuvant RT	Very Low
Genitourinary Symptoms	3	1,008	RR: 1.65; 95% CI 1.20,2.27	Significant harm with adjuvant RT	Very Low
Erectile Dysfunction	2	583	RR: 1.02; 95% CI 0.98,1.05	Equivalent	Very Low
Overall	3	2,599	RR: 1.63; 95% CI 1.11,2.40	Significant harm with adjuvant RT	Very Low

CoE: Certainty of Evidence
CI: confidence interval
PFS: progression-free survival
RCT: randomized controlled trial
RR: risk ratio
RT: radiotherapy

Androgen deprivation therapy and radiotherapy versus androgen deprivation therapy alone for locally-advanced prostate cancer with extra-prostatic extension but no lymph node involvement

Recommendation

4. Among patients with locally advanced prostate cancer with extra-prostatic extension but no lymph node involvement, we recommend to give androgen deprivation therapy and radiotherapy over androgen deprivation therapy alone.
Certainty of Evidence: Very low
Strength of Recommendation: Strong

Among the patients with newly-diagnosed prostate cancer, 10-20% belongs to the locally-advanced or high-risk category with relatively higher relapse rates [38]. The National Comprehensive Cancer Network Clinical Guidelines in Oncology defines high-risk disease as a tumor with extra-prostatic extension (T3a), a grade group of 4 or 5, or a PSA level $\geq$20 ng/mL [39].

As prostate cancer is primarily hormone-driven, androgen deprivation therapy (ADT) is part of the standard-of-care for high and very high risk groups. Radiotherapy (RT) is also commonly used.

Evidence to Decision

Benefit and Harm

Three RCTs (n=2,343) described in eight articles compared the use of ADT and RT versus ADT alone. Pooled data showed significant benefit with the use of ADT and RT in reducing all-cause mortality (RR: 0.80; 95% CI; I^2=0%) and prostate cancer-specific mortality (RR: 0.48; 95% CI 0.40, 0.57 I^2=0%) [40-42] (Table 10). The combination of ADT and RT also showed higher 8- and 10-year progression-free survival rates (range of 48% [95% CI 39%, 56%] to 74%, [95% CI 68%, 78%]) than with ADT alone (range of 7%, [95% CI 3% to 12%] to 46% [95% CI 41% to 51%]) [41,42]. ADT and RT were also beneficial in decreasing the hazard of progression after a median of 8 years (HR: 0.31; 95% CI 0.27, 0.37) [41,43].

Adverse events were infrequent in the two treatment groups. More genitourinary (12% vs. 1%, p<0.001) and gastrointestinal symptoms (17% vs 1%, p<0.001) were noted in the ADT and RT combination arm compared to those given ADT only. There was no significant difference in the urinary and sexual function, and cardiovascular complications between the two treatment groups at 24 months, however, there were milder gastrointestinal symptoms reported in the ADT and RT group [42,44,46].

Analysis of the health-related QOL using the Functional Assessment of Cancer Therapy-Prostate Questionnaire (FACT-P) questionnaire showed that total scores were comparable (mean score 121.5) at baseline. The combination of ADT and RT resulted in a worse QOL score for the physical (mean difference: -1.1 vs -2.1, p-value=0.001) and functional well-being (mean difference: -3.2 vs. -6.4, p=

0.004), and for the prostate cancer subscale (mean difference: -0.1 vs. -2.4, p-value <0.001) at 6 months. These differences may reflect treatment-related toxicities from RT. However, the large differences in QOL scores tapered out and at 12 and 36 months, there was no significant difference in QOL scores between the combination and the ADT arms [44,45].

Disease-specific urinary, bowel, and sexual functions were assessed using the Prostate Cancer Symptom Scale (PCSS). The results were comparable between both groups for the gastrointestinal, genitourinary, and sexual functions at baseline. In the combination arm, the genitourinary symptoms worsened (mean difference of 2.5, p<0.001) but were back to near baseline status at 3 months (mean difference from baseline of 0.5, p=0.001) and after 4 years (mean difference: 0.10, p=0.019) after RT. Overall bowel symptoms worsened for both the combination and ADT arms at 3 months. Bowel symptoms worsened after radiotherapy in the combination arm (mean difference: 2.6, p<0.001), whereas it worsened after 3 months in the ADT arm alone (mean difference: 0.6, p=0.002). The scores remained significantly worse after 4 years in the ADT and RT group, whereas it approached baseline after 4 years of follow-up in the ADT group (mean difference: 0.30, p<0.0001). Sexual function worsened from baseline to 3 months for both the ADT and RT (mean difference of 3 p<0.001) and ADT groups (mean difference of 3.5 p<0.001) and remained at this status until the end of 4-year follow-up [46].

The CoE for all outcomes was downgraded due to risk of bias and indirectness. The CoE for outcomes on health-related QOL, gastrointestinal, genitourinary, and sexual function symptoms, and treatment-related toxicities was downgraded further due to inconsistency.

Other Considerations

Cost

There was no local cost-effectiveness study on the use of ADT and radiotherapy. If the drug regimen used in the TAP32 trial [42] would be applied locally, the yearly treatment cost (flutamide for one month and four doses of leuprorelin 11.25 mg) would be Php 174,076.00. The full cost after three years of ADT alone would be in the range of Php 414,316.00. Both treatment arms have ADT, which amounts to a bigger cost. Table 4 under Key Question 1 lists the costs of radiotherapy modalities. Refer to Key Question 2, Table 6 for the annual treatment cost of locally available ADTs.

Other Guidelines

NCCN recommends the use of ADT for high and very high-risk disease, unless medically contraindicated. EBRT and brachytherapy are recommended in conjunction with ADT, either before, during, or after ADT in patients with an expected survival of >5 years or otherwise symptomatic. ADT may be given as LHRH agonist alone, LHRH agonist plus a first-generation anti-androgen, or LHRH antagonist, but never as monotherapy in patients with clinically localized disease, unless there is a contraindication to definitive therapy (life expectancy is </5 years or substantial comorbidities). Radical prostatectomy with pelvic lymph node dissection may be considered for younger, healthier patients without tumor fixation to adjacent pelvic side-wall [47].

Consensus Issues

For the population of concern in this question, the goal is still cure. The evidence showed that the possibility of cure is higher with the combination of ADT and RT and the resulting side effects may still be acceptable to patients. If RT is not administered, we lose the window of opportunity for cure among those who underwent radical prostatectomy. For many surgeons, the decision to proceed with surgery depends a lot on the possibility of cure so RT is already planned pre-operatively.

There was difficulty in reaching a consensus regarding the strength of recommendation due to concerns about the adverse effects of RT. The specific RT protocols used in the reviewed RCTs and those available in the country were clarified. The types and the doses of EBRT given in the 3 RCTs varied (Table 8). The four field box technique used by Mason et. al. and Sargos et. al. is a conventional type of RT that usually covers the whole pelvis field in the 45-46 Gy dose then with 3DCRT for the prostate with target volume/prostate boost for 20-24 Gy or 20-28 Gy. RT used by Fossa 2015 was pure 3d conformal. In local practice, newer modes of EBRT are available. A dose of at least 70 Gy in 35 fractions using IMRT or IGRT is used in treating the prostate definitively. Using conventional RT (3DCRT), a dose of 60 Gy only can be given to the patient because of its potential toxicities to the bowel, bladder, and femur. IMRT-based treatment is commonly used in private institutions, but most government hospitals are still using 3DCRT. The higher cost and limited availability of newer types of EBRT associated with lower adverse effects may worsen health inequity. As with previous recommendations, the cost implications need to be studied and patients should be well informed of their treatment options and the benefits, cost, and adverse effects of these treatments.

Table 9. Types of RT and doses given in the RCTs reviewed for Key Question 4

Study	Type of radiotherapy	Dose of radiotherapy
Mason et al 2015	Four-field box technique to cover prostate, seminal vesicles,and internal and external iliac lymph nodes	Pelvic target volume: 45 Gy given in 25 fractions over 5 weeks Prostate target volume: 20-24 Gy given in 10-12 fractions over 2-2.5 weeks (at investigator's discretion)
Fossa 2015	Standard 3D conformational RAD using customized blocks	Minimum 70 Gy to prostate and 50 Gy to seminal vesicles(protocol amended to increase total dose to 74-78 Gy, received by 27 out of 436 in intervention arm, 6%)
Sargos 2019	Four-field technique for the pelvic volume and a four- or six-field technique for the prostatic volume using high-energy photons (>10 Mv) and 3D computed tomography planning	Whole pelvis: 462 Gy in 25 fractions over 5 weeks Prostate boost: 20-28 Gy delivered in 10-12 fractions over 15-20 days

Table 10. Summary of outcomes for Key Question 4

OUTCOME	NO. OF INCLUDED RCTs	n	EFFECT MEASUREMENT [95%CI]	INTERPRETATION	CoE
All-cause mortality	3	2,343	RR: 0.80; 95% CI 0.73,0.88	Significant benefit with ADT+RT	Moderate
Prostate cancer-specific mortality	3	2,343	RR: 0.48; 95% CI 0.40,0.57	Significant benefit with ADT+RT	Moderate
Progression-free survival					
8 year PFS	2	1,468	48% (39% to 56%) vs 7% (3% to 12%)	Significant benefit with ADT+RT	High
10 year PFS			74% (95% CI: 68% to 78%) vs. 46% (95% CI: 41% to 51%)	Significant benefit with ADT+RT	
Time-to-disease progression					
6 year median follow-up	1	1,205	HR: 0.30; 95% CI: 0.23,0.39	Significant benefit with ADT+RT	High
8 year median follow-up			HR:0.31; 95% CI: 0.27,0.37		
Health-related QOL	1	1,205	Worse quality-of-life in terms of physical and functional well-being, as well as prostate cancer-specific symptoms in the first 6 months for the ADT+RT group. At 12 and 36 months, however, quality-of-life scores are similar for both the intervention and control arm.		Moderate
Disease-specific urinary, bowel, and sexual functions (follow-up: median 4 years)	1	875	There were modest symptoms for both intervention and control groups, at baseline. Genitourinary symptoms worsened following radiotherapy, and improved following ADT alone. Bowel and sexual function symptoms worsened across both arms.		Moderate
Adverse Events					

6 months	3	2,343	Higher risk of genitourinary and gastrointestinal symptoms in the intervention arm	Low
24 months			Urinary symptoms were comparable between the two groups No difference between the ADT+RT and ADT group in terms of sexual function and cardiovascular Individuals in the combination arm had a higher risk for gastrointestinal problems, although majority were mild (RR: 1.90, 2.85)	

ADT: androgen deprivation therapy
CoE: Certainty of Evidence
CI: confidence interval
HR: hazards ratio
QOL: quality of life
RCT: randomized controlled trial
RR: risk ratio
RT: radiotherapy

Use of docetaxel, abiraterone, or radiation in addition to androgen deprivation therapy for newly-diagnosed prostate cancer with M1 metastasis

Recommendation

5. Among patients with newly-diagnosed prostate cancer and M1 metastasis, either asymptomatic with high or very high-risk features of disease, or symptomatic regardless of risk,
   5a. we suggest the addition of docetaxel alone or abiraterone alone
   5b. we suggest against adding EBRT to ADT.

Certainty of Evidence: Very low
Strength of Recommendation: Weak

ADT is the core management for metastatic castration-sensitive prostate cancer [48]. Although most patients favorably respond initially to these agents, the majority progress to castrate-resistant prostate cancer (CRPC) within one year [49-51]. Compared to the favorable prognosis of locally-advanced prostate cancer, the relative survival rate of metastatic disease is only 30% [52]. Newer chemotherapy and hormonal agents such as docetaxel and abiraterone, respectively, and EBRT are available as additional treatment options to improve survival.

Evidence to Decision

Benefit and Harm

ADT + Docetaxel versus ADT alone

There was significant benefit with the use of ADT and docetaxel over ADT alone in improving overall survival (HR: 0.77; 95% CI 0.68,0.87; I^2=0%) and time to castrate-resistant prostate cancer (CRPC) (HR: 0.61; 95% CI 0.52, 0.73) [53-55] (Table 11). However, more adverse events were reported with the use of the combination. These adverse events were neutropenia (RR: 34.48; 95% CI 6.32,188.17; I^2=43%); febrile neutropenia (RR: 11.73; 95% CI 6.90,19.94; I^2=0%); dermatologic adverse events (RR: 15.42; 95% CI 2.00,119.04; I^2=0%); gastrointestinal (RR: 2.54; 95% CI 1.67,3.87; I^2=0%), pulmonary (RR: 2.24; 95% CI 1.35,3.72; I^2=0%), nervous system and peripheral neuropathy (RR: 2.01; 1.09,3.68; I^2=0%) and general disorders (RR: 2.59; 95% CI 0.63, 10.70; I^2=72%) [53,54]. There was no significant difference in the QOL between the two groups.

ADT + Abiraterone versus ADT alone

There was significant benefit with the use of abiraterone and ADT over ADT alone in terms of overall survival (HR: 0.64; 95% CI 0.56, 0.73 I^2=0%) and progression-free survival (HR: 0.45; 95% CI 0.40, 0.51) [56,57]. However, the following adverse effects were increased in the combination arm: death (RR: 1.67; 95% CI 1.05 2.64; I^2=0%); hypokalemia (RR: 6.28; 95% CI 3.52,11.21; I^2=0%); hepatic dysfunction (RR: 4.51; 95% CI 2.79,7.29; I^2=31%); increase in blood pressure (RR: 2.48; 95% CI 1.53,4.03; I^2=56%), respiratory events

(RR: 2.08; 95% CI 1.33,3.25; I^2=0%), cataracts (RR: 8.07; 95% CI 1.01,64.03), and cardiovascular events (RR: 2.02; 95% CI 1.19,3.44; I^2=0%) [55,56]. Treatment with abiraterone and prednisone on top of ADT improved pain and fatigue as well as overall health-related QOL compared to ADT alone.

ADT + EBRT versus ADT alone

There was no significant difference in the overall survival (HR: 0.92; 95% CI 0.81, 1.05) and occurrence of adverse events between the ADT and EBRT arm versus ADT arm alone [58,59]. Moreover, there was a significant increase in urinary symptoms and diarrhea at 3 months and 22% of the patients reported persistent bowel changes after two years in the combination group.

Other Considerations

Cost

There was no local cost-effectiveness study on the aforementioned interventions. The annual treatment cost of abiraterone 250 mg and 500 mg tablet is Php 1,093,680.00 and Php 1,074,000.00, respectively. The cost of radiotherapy and ADTs can be found in Tables 4 (Key Question 1) and 6 (Key Question 2).

Other Guidelines

ESMO recommended the use of ADT as first-line treatment of metastatic hormone-sensitive prostate cancer (HSPC) in combination with abiraterone/prednisone or apalutamide or docetaxel or enzalutamide. Radiation to the primary tumor combined with systemic treatment is recommended for patients with low-volume mHNPC. ADT alone is recommended as first-line systemic treatment of mHNPC in men who are unfit for abiraterone, apalutamide, enzalutamide, and docetaxel [60].

NCCN recommended the use of ADT with either apalutamide, abiraterone, docetaxel for 6 cycles, and enzalutamide. EBRT to the primary tumor with low volume M1 or ADT alone was also recommended [61].

AUA recommended the use of either ADT with either LHRH agonists or antagonists or surgical castration is recommended among patients with mHSPC. Among patients with mHSPC, ADT in combination with either androgen pathway-directed therapy (i.e., abiraterone acetate plus prednisone, apalutamide, enzalutamide) or chemotherapy (docetaxel) may also be given. Among mHSPC patients with low-volume metastatic disease, primary radiotherapy to the prostate and ADT may also be offered [62].

Consensus Issues

The data that may directly answer the key question on the addition of triplet therapy with docetaxel, abiraterone, and EBRT to ADT are not yet published (PEACE-1 Trial) and may later provide an important update to this recommendation. The preliminary results showed that the addition of abiraterone to the standard of care (both ADT alone or ADT plus docetaxel) improved overall survival, especially among patients with high-volume metastases.

For clarity, the panel preferred separate recommendations for docetaxel, abiraterone, and EBRT as additional treatments to ADT. The importance of determining the effect of interventions on quality of life was discussed. An additional benefit of improved QOL will be an improved compliance to treatment. However, the limitations in measuring QOL need to be carefully considered. It is difficult to exactly quantify the QOL for certain patients, for example, those who are paralyzed or in a vegetative state.

Table 11.1 Summary of outcomes for Docetaxel + ADT versus ADT alone

OUTCOME	NO. OF INCLUDED RCTs	n	EFFECT MEASUREMENT [95%CI]	INTERPRETATION	CoE
Overall survival	3	2,261	HR 0.77; 95% CI 0.68, 0.87	Significant benefit with docetaxel+ADT	Moderate
Time to castration-resistant prostate cancer	3	790	HR 0.61; 95% CI 0.52, 0.73	Significant benefit with docetaxel+ADT	Moderate
Adverse events					
Neutropenia	2	215	RR: 34.48; 95% CI 6.32,188.17	Significant harm with docetaxel+ADT	Very low
Febrile neutropenia	2	215	RR: 11.73; 95% CI 6.90,19.94	Significant harm with docetaxel+ADT	Very low
Dermatologic symptoms	2	215	RR: 15.42; 95% CI 2.00,119.04	Significant harm with docetaxel+ADT	Very low
Gastrointestinal symptoms	2	215	RR: 2.54; 95% CI 1.67,3.87	Significant harm with docetaxel+ADT	Very low
Pulmonary symptoms	2	215	RR: 2.24; 95% CI 1.35,3.72	Significant harm with docetaxel+ADT	Very low
Nervous system and peripheral neuropathy	2	215	RR: 2.01; 95% CI 1.09, 3.68	Significant harm with docetaxel+ADT	Very low
	2	215		Significant harm with docetaxel+ADT	Very low
General disorders	2	215	RR: 2.59; 95% CI 0.63,10.70	Significant harm with docetaxel+ADT	Very low
QOL	2	1,098	Using the FACIT-Fatigue, patients on the intervention arm had clinically significant lower scores at 3 months than did patients on ADT monotherapy. Findings did not meet the minimal clinically important difference between the two arms using FACT-P. Brief Pain Inventory and FACT-Taxane scores did not differ between the		Low

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	two arms. There was no clinically significant difference between the two group except for constipation which was more common in the docetaxel arm using EORTC QLQ30.

ADT: androgen deprivation therapy
CoE: Certainty of Evidence
CI: confidence interval
HR: hazards ratio
QOL: quality of life
RCT: randomized controlled trial
RR: risk ratio

Table 11.2 Summary of outcomes for Abiraterone + ADT versus ADT alone

OUTCOME	NO. OF INCLUDED RCTs	n	EFFECT MEASUREMENT [95%CI]	INTERPRETATION	CoE
Overall survival	2	2,201	HR: 0.64; 95% CI 0.56,0.73	Significant benefit with abiraterone+ADT	Moderate
Time to castration-resistant prostate cancer	1	790	HR: 0.45; 95% CI 0.40,0.51	Significant benefit with abiraterone+ADT	Low
Adverse events					
Death	2	3,107	RR: 1.67; 95% CI 1.05, 2.64	Significant harm with abiraterone+ADT	Very low
Hypokalemia	2	3,107	RR: 11.73; 95% CI 6.90,19.94	Significant harm with abiraterone+ADT	Very low
Hepatic dysfunction	2	3,107	RR: 4.51; 95% CI 2.79,7.29	Significant harm with abiraterone+ADT	Very low
HTN and increase in blood pressure	2	3,107	RR: 2.48; 95% CI 1.53 4.03	Significant harm with abiraterone+ADT	Very low
Respiratory symptoms	2	3,107	RR: 2.08; 95% CI 1.33,3.25	Significant harm with abiraterone+ADT	Very low
Cataracts	2	3,107	RR: 8.07; 95% CI 1.01,64.03	Significant harm with abiraterone+ADT	Very low
Cardiovascular events	2	3,107	RR: 2.02; 95% CI 1.19, 3.44	Significant harm with abiraterone+ADT	Very low

QOL	1	1,146	Abiraterone plus ADT improved pain and fatigue as well as overall health-related QOL compared to ADT alone. EQ-5D-5L data indicated better general health status scores (assessed by the EQ-VAS) and health utility scores in patients in the ADT plus abiraterone acetate and prednisone group than in patients in the ADT plus placebo group.	Low

ADT: androgen deprivation therapy
CoE: Certainty of Evidence
CI: confidence interval
HR: hazards ratio
QOL: quality of life
RCT: randomized controlled trial
RR: risk ratio

Table 11.3 Summary of outcomes for EBRT + ADT versus ADT alone

OUTCOME	NO. OF INCLUDED RCTs	n	EFFECT MEASUREMENT [95%CI]	INTERPRETATION	CoE
Overall survival	2	2,123	HR: 0.92; 95% CI 0.81,1.05	Inconclusive	Moderate
Adverse events	1	2,035	There was no significant difference in adverse events between the group given EBRT and ADT compared to ADT alone.		Very low
QOL	1	423	Only an increase in diarrhea at 3 months reached clinical significance. While some patients reported transient urinary and bowel symptoms, 22% of them reported persistent bowel changes after two years based on the QLQ-PR25 questionnaire. The presence of urinary symptoms at 3 months was clinically significant as well.		Low

CoE: Certainty of Evidence
CI: confidence interval
HR: hazards ratio
QOL: quality of life
RCT: randomized controlled trial

Androgen deprivation therapy and radiotherapy for castration-sensitive metastatic prostate cancer with low metastatic burden

Recommendation

6. Among patients with castration-sensitive metastatic prostate cancer with low metastatic burden (<5 bone metastases), we suggest androgen deprivation therapy and radiotherapy to the primary tumor.
Certainty of Evidence: Very low
Strength of Recommendation: Weak

Prostate cancer typically metastasizes to the bones [63]. Combining androgen-deprivation therapy (ADT) with RT may reduce tumor volume and improve local tumor control by preventing repopulation [64]. RT may also cause metastatic sites to shrink probably due to immune mechanisms (i.e., "abscopal effect") [63].

Evidence to Decision

Benefit and Harm

Two RCTs (n=2,493) [65,66] investigated the effectiveness and safety of combining radiotherapy (RT) to the primary tumor with androgen deprivation therapy (ADT) versus ADT alone among patients with castration-sensitive metastatic prostate cancer (mPC) with <5 bone lesions. Pooled results showed no significant difference in progression-free survival (RR: 0.92; 95% CI 0.81, 1.05, I^2 = 0%) between treatment groups (Table 11). The overall survival in the RT+ADT group was as good as or better than the ADT arm alone (RR: 0.82; 95% CI: 0.68, 0.99, I^2 = 0%). The addition of EBRT reduced deaths attributable to prostate cancer (RR: 0.66; 95% CI 0.49, 0.90) among patients with low-volume metastatic disease [65].

One study (n=2,035) reported adverse events which were classified using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [65]. About one-third of patients reported at least one severe adverse event with CTCAE grade 3 or worse (RT+ADT group: 39%; ADT only group: 38%). The risk of developing at least one severe adverse event was not significantly different between treatment arms (RR: 1.02; 95% CI 0.91, 1.14). Grade 3-5 toxicities were not significantly different for endocrine (14.2% vs. 14.5%), musculoskeletal (9.2% vs. 8.6%), renal (5.0% vs. 4.1%) nor blood/bone marrow (3.8% vs. 4.8%) adverse events. No deaths attributed to treatment were reported. Among those assigned to receive RT with safety data (n=920), 48 (5%) developed at least one grade 3-4 Radiation Therapy Oncology Group (RTOG) adverse event including diarrhea, proctitis, cystitis, and hematuria.

The RT+ADT arm has significantly higher bowel symptom scores (range: 0 to 92) than the ADT arm alone at 12 months (MD: 3.1; 95% CI 0.5, 5.8, p=0.022) and 24 months (MD: 8.0; 95% CI 4.8, 11.1, p < 0.001) indicating worse QOL.

Differences in other QOL domains for 6, 12- and 24-month follow-ups were not significantly different [66].

The overall certainty of evidence was downgraded to low due to imprecision and indirectness with regards survival outcomes and serious risk of bias and indirectness with QOL outcomes.

Other Considerations

Cost

There was no local cost-effectiveness on the use of ADT+RT and ADT alone. If the alternative regimen in the STAMPEDE trial (2.75 Gy x 20 daily fractions) will be adapted, this will amount to around Php 140,000.00 [65]. Case rates for radiotherapy are listed in Table 4 under Key Question 1.

Other Guidelines

ESMO recommends a combination of RT to the primary tumor and systemic treatment for patients with low-volume metastatic hormone-naïve prostate cancer based on the STAMPEDE and HORRAD data [67]. NCCN states that RT to the prostate is an option for prostate cancer patients with low-volume castration-naive metastatic disease in the absence of contraindications. The NCCN guideline panel does not recommend dose escalation beyond 55 Gy in 20 fractions (moderate hypofractionation), 6 Gy x 6 fractions (ultra-hypofractionation) or their biologic equivalents because of increased toxicity [68].

Consensus Issues

The concept of hypofractionated radiation was discussed. Hypofractionation pertains to the administration of high doses of radiation (200 cGy or 2 Gy per session) over a shorter period of time compared to the standard dose. Similar with the previous discussions, the concerns on high cost of and limited availability of the interventions that may worsen health inequity and the lack of cost-effectiveness study were raised.

Table 12. Summary of outcomes for Key Question 6

OUTCOME	NO. OF INCLUDED RCTs	n	EFFECT MEASUREMENT [95%CI]	INTERPRETATION	CoE
Overall survival	2	963	RR: 0.82; 95% CI 0.68,0.99	As good as or better than ADT alone	Low
Progression-free survival	2	963	RR: 0.92; 95% CI 0.81,1.05	Inconclusive	Low
Prostate cancer-specific survival	1	819	RR: 0.66; 95% CI 0.49,0.90	Significant benefit with ADT+RT	High
Adverse events					
Endocrine symptoms	1	2,035	RR: 0.98; 95% CI 0.79,1.21	Inconclusive	Moderate
Musculoskeletal symptoms	1	2,035	RR: 1.08; 95% CI 0.82,1.42	Inconclusive	Moderate
Renal dysfunction	1	2,035	RR: 1.22; 95% CI 0.21,1.81	Inconclusive	Moderate
Blood/bone marrow-related symptoms	1	2,035	RR: 0.79; 95% CI 0.52,1.20	Inconclusive	Moderate
QOL	1	432	Bowel symptom scores (0 to 92 scale) were worse with RT+ADT group than ADT alone: • 12 months - MD 3.1 (95% CI: 0.5 to 5.8) • 24 months - MD 8.0 (95% CI: 4.8 to 11.1) Differences in other domains for 6-, 12- and 24-month follow-ups were not significantly different.		Very low

ADT: androgen deprivation therapy
CoE: Certainty of Evidence
CI: confidence interval
MD: mean deviation
QOL: quality of life
RCT: randomized controlled trial
RR: risk ratio
RT: radiotherapy

Systemic chemotherapy with or without androgen deprivation therapy for metastatic castrate-resistant prostate cancer

Recommendation

7. Among patients with metastatic castrate-resistant prostate cancer, we suggest systemic chemotherapy with or without androgen deprivation therapy. However, we suggest resuming androgen deprivation therapy if serum testosterone increases above 50 ng/dL.
Certainty of Evidence: Very low
Strength of Recommendation: Weak

Androgen deprivation therapy is the usual first-line treatment for patients with advanced prostate cancer [69,70]. However, cancer may still progress despite therapy. Patients with castrate levels of serum testosterone <50ng/dL and an increase in prostate-specific antigen (PSA), local progression, new metastases or worsening of preexisting metastases are diagnosed to have castrate-resistant prostate cancer (CRPC). For these patients, other systemic therapy may be considered and the net benefit of continuing ADT is uncertain. Suspension of ADT with serum testosterone monitoring is an alternative treatment option.

Evidence to Decision

Benefit and Harm

One randomized non-inferiority trial (n=198) compared survival, adverse events, and QOL after suspension or maintenance of ADT among patients with metastatic castrate-resistant prostate cancer (mCRPC) given systemic therapy (either chemotherapy or non-chemotherapy) [71].

There was no apparent difference in overall survival (HR: 0.98; 95% CI 0.72,1.33) and biochemical progression-free survival (1.13; 95% CI 0.85,1.51) between the ADT suspension or maintenance groups (Table 13). For the outcome of clinical/radiographic progression-free survival (c/rPFS), suspension of ADT is non-inferior to maintenance of ADT (HR: 0.98; 95% CI 0.73,1.31). In the ADT suspension group, survival data at 3 months were compared according to serum testosterone levels (i.e., castrate levels [n=79] and above castrate levels of testosterone [n=19]). The effect estimates for overall survival (HR: 0.75; 95% CI 0.46, 1.3), c/rPFS (HR: 1.4; 95% CI 0.61,1.77), and bPFS (HR: 0.75; 95% CI 0.44, 1.30) were all inconclusive.

There was no conclusive difference in adverse event rates in the ADT suspension and maintenance groups. The most common adverse events were fatigue, gastrointestinal-related symptoms, and neutropenia.

There was no statistically significant difference in QOL, measured through the FACT-P questionnaire, between the two study groups [71].

The certainty of evidence was downgraded to very low for all outcomes due to risk of bias, inconsistency, and imprecision.

Other Considerations

Cost

There is currently no local cost-effectiveness on the suspension and maintenance of ADT. Refer to Table 6, Key Question 2 for the annual treatment cost of ADTs.

Other Guidelines

NCCN recommends continuation of ADT to maintain castrate levels of serum testosterone at <50ng/dL for patients with CRPC with imaging studies positive for metastases. Preferred treatment is continuation of LHRH agonists or degarelix while additional therapies like hormone therapy (androgen metabolism inhibitors like abiraterone, or first-generation antiandrogens like flutamide or bicalutamide) are given [69]. The Canadian Urological Association (CUA)-Canadian Uro Oncology Group (CUOG), AUA, and ASCO recommends continuation of ADT for nonmetastatic CRPC but has no recommendations regarding ADT in patients with metastatic disease [72-74].

Consensus Issues

Monitoring of testosterone levels is a vital part of the clinical management of patients with mCRPC. A baseline value is obtained prior to ADT, then every 6 or 12 months while on ADT. Testosterone levels above the castrate level (50ng/dl) indicate that treatment with ADT is inadequate or unsuccessful. On the other hand, those able to maintain castrate-level testosterone, especially the elderly who already have testicular atrophy, may opt to suspend the use of ADT. Given this notion that elderly patients who had received ADT and maintain castrate levels of testosterone will not regain normal testosterone levels, this cannot be applied to all patients.

In the Philippines, many urologists believe that the safest way to proceed is to simply maintain the ADT. One panelist noted that the additional cost of maintaining ADT is worth it. Aside from keeping testosterone at castrate level, it also controls other pathways involved in disease progression. In the reviewed RCT, 19/98 (9.3%) had an increase in testosterone at 3 months after suspension of ADT.

The current standard of care worldwide is to maintain ADT (continuous or intermittent) for patients with mCRPC. Clinicians who discontinue ADT do so intermittently after at least 6 months of use, when undetectable PSA level is reached and once an additional systemic agent (chemotherapy or novel hormonal agent) is already started. The trigger for resumption is arbitrarily a rise of PSA level >4 ng/ml. However, this level is not yet clearly defined which is why the vast majority of clinicians opt to just maintain ADT.

To date, there is no documented ADT resistance associated with the intermittent administration of ADT. The intermittent administration of ADT is cost-saving and reduces the occurrence of adverse events.

Table 13. Summary of outcomes for Key Question 7

OUTCOME	NO. OF INCLUDED RCTs	n	EFFECT MEASUREMENT [95%CI]	INTERPRETATION	CoE
Biochemical progression-free survival	1	198	HR: 1.13; 95% CI 0.85,1.51	Inconclusive	Very low
Clinical/radiographic progression-free survival	1	198	HR: 0.98; 95% CI 0.73,1.31	Suspension of ADT is non-inferior to maintenance of ADT	Very low
Overall Survival	1	198	HR: 0.98; 95% CI 0.72,1.33	Inconclusive	Very low
Adverse Events	1	198	No significant difference between the two arms. Most common toxicities include gastrointestinal symptoms (nausea, vomiting and diarrhea) (39.6% in Arm A; 40.2% in Arm B), fatigue (38.6% in Arm A; 48.1% in Arm B) and neutropenia (26% in Arm A; 23.3% in Arm B)		Very low
QOL	1	198	No significant difference between groups using the FACT-P questionnaire		Very low

ADT: androgen deprivation therapy *Arm A: ADT maintenance* *Arm B: ADT suspensin*
CoE: Certainty of Evidence
CI: confidence interval
HR: hazard ratio
QOL: quality of life
RCT: randomized controlled trial
RT: radiotherapy

Use of bone-modifying agent and radiotherapy for prostate cancer with bone metastases

Recommendation

8. Among prostate cancer patients with bone metastases, we suggest against the addition of a bone-modifying agent to radiotherapy.
Certainty of Evidence: Very low
Strength of Recommendation: Weak

Radiation therapy remains the treatment of choice for prostate cancer with localized bone metastases resistant to systemic therapy [75]. Bone-modifying agents such as bisphosphonates and RANK-ligand inhibitors are used to reduce skeletal-related events (SREs) due to cancer and androgen deprivation therapy-induced bone resorption [75]. The effect of adding these bone-modifying agents to radiotherapy among prostate cancer patients with bone metastases is not established.

Evidence to Decision

Benefit and Harm

There is no study that directly evaluated the effect of bone-modifying agents and radiotherapy compared to radiotherapy alone in reducing skeletal-related events (SRE) and improving overall survival among prostate cancer patients with bone metastases. There is one RCT that provides indirect evidence [76] on the comparison of ibandronate and radiotherapy. There was no significant difference between the two groups in terms of pain response at four weeks (MD: -3.7%; 90% CI -12.4%, 5.0%, p=0.49) and at 12 weeks (MD: 6.7%; 90% CI -2.6%, 16.0%, p=0.24) (Table 14). Likewise, there was also no significant difference in the risk of pathological fractures (ibandronate 3% vs. RT 2%, p=0.31, RR: 1.4; 95% CI 0.451, 4.35). There was a similar risk of spinal cord compression (ibandronate 5.6% vs. RT 3.3%, p=0.19, RR: 1.714; 95% CI 0.687,4.278) between the two groups. The median overall survival in ibandronate group was slightly higher at 12.9 months (95% CI 11.1, 14.2), versus 12.2 months (95% CI 10.1, 14.1) in the radiotherapy group (HR: 0.89; 95% CI 0.73, 1.09, p=0.25). The median survival of patients who were given subsequent ibandronate treatment after unsuccessful pain control from radiotherapy was higher (12.7 months, 95% CI 7.9, 15.3 months), compared to patients who underwent radiotherapy (11.8 months, 95% CI 10.0, 14.2 months).

The risk of any occurrence of adverse events in the ibandronate group was not significantly higher than in the radiotherapy group (RR: 0.938; 95% CI 0.752, 1.171, p=0.572). However, the incidence of diarrhea was significantly higher in the radiotherapy group (6% vs. 12%, p=0.014; RR: 0.464, 95% CI 0.247, 0.874) [76]. In terms of nausea, the ibandronate group has reduced or similar risk compared with the radiotherapy group (18% vs. 26%, p=0.058; RR 0.717, 95% CI 0.506, 1.014).

There was no significant difference in QOL between the two groups, at four weeks the mean difference was -1.0 (99% CI -4.0, 2.0, p=0.37), and -0.3 (99% CI -3.8,

3.3, p=0.84) at 12 weeks. Only the social well-being domain at 12 weeks showed a significant difference of 1.0 (99% CI -0.2, 2.1, p=0.03) between ibandronate (mean change-from-baseline 0) and radiotherapy (mean change-from-baseline -1.0) [76].

Other Considerations

Cost

There is no local cost-effectiveness study in the Philippines on the use of radiation therapy or bone-modifying agents for bone metastases. Ibandronate 6 mg/mL and zoledronic acid 4 mg/mL are given every 4 weeks and denosumab 60 mg/mL at 120mg/dose is given every 4 weeks. The annual cost of treatment using ibandronate 6mg/6mL vial costs Php 92,100.00 – Php 129,147.12. Annual treatment cost using zoledronic acid 4 mg/vial ranges from Php 42,000.00 – Php 168,000.00, and denosumab 60 mg/mL, 1 mL pre-filled syringe costs Php 232,224.00 – Php 325,516.80 [77]. The cost of different radiotherapy modalities are tabulated in Table 4, Key Question 1.

Other Guidelines

ESMO, ASCO, and Cancer Care Ontario (CCO) uniformly recommend that either zoledronic acid or denosumab may be given to prevent or delay SREs in patients with metastatic castration-resistant prostate cancer [75,78,79]. However, none of these guidelines recommend combining bone-modifying agents with radiation therapy to treat bone metastases. The Philippine Society of Medical Oncology (PSMO) consensus recommendations on prostate cancer management prioritization during the COVID-19 pandemic do not mention the use of bone-modifying agents as an add-on therapy to radiotherapy for bone metastases [80].

Consensus Issues

Clinicians aim to prevent bone metastases because it usually results in debilitating pain and sometimes, neurologic complications. On the other hand, there are some patients with bone metastases who experience a lesser level of pain. Radiotherapy is done for patients who have spinal cord compression and experience debilitating pain. However, radiotherapy cannot be given to all affected areas if these are multiple. The priority are weight-bearing areas (pelvic and lumbar areas), areas that are painful, and neurologic deficits. Both radiotherapy and bone-modifying drugs do not improve overall survival because they are non-systemic agents, hence only help in reducing skeletal-related events (i.e., pain palliation, reversal of cord compression). Further evidence is needed for this recommendation.

Table 14. Summary of all outcomes for Key Question 8

OUTCOME	NO. OF INCLUDED RCTs	n	EFFECT MEASUREMENT [95%CI]	INTERPRETATION	CoE
Pain score					
At 4 weeks	1	470	MD: -3.7%; 90% CI -12.4%,5.0%, *p*=0.49	Inconclusive	Very low
at 12 weeks	1	470	MD: 6.7%; 90% CI -2.6%,16.0%, *p*=0.24	Inconclusive	Very low
Occurrence of pathological fracture	1	470	RR: 1.40; 95% CI 0.45,4.34	Inconclusive	Very low
Occurrence of spinal cord compression	1	470	RR: 1.71; 95% CI 0.69,4.28	Inconclusive	Very low
Overall survival	1	470	HR: 0.89; 95% CI 0.73,1.09	Significant benefit with ibandronate	Very low
Adverse events	1	470	RR: 0.94; 95% CI 0.75,1.17	Inconclusive	Very low
Diarrhea	1	470	RR: 0.464; 95% CI 0.247, 0.874	Significant harm with ibandronate	Low
Nausea	1	470	RR: 0.717; 95% CI 0.506, 1.014	Ibandronate group with reduced or similar risk with RT	Very low
Overall QOL	1	470	MD in overall QOL between ibandronate vs RT at 4 weeks: -1.0 (99% CI -4.0 to 2.0, p=0.37), and at 12 weeks: -0.3 (99% CI -3.8 to 3.3, p=0.84).		Very low

CI: confidence interval
CoE: Certainty of Evidence
HR: hazard ratio
MD: mean deviation
RR: risk ratio
RT: radiotherapy
QOL: quality of life

Prostate biopsy versus watchful waiting for patients with single elevated prostate-specific antigen and normal digital rectal exam

Recommendation

9. Among patients with single elevated prostate-specific antigen and normal digital rectal exam, we suggest watchful waiting with risk factor assessment and serial PSA monitoring over doing a prostate biopsy
Certainty of Evidence: Very low
Strength of Recommendation: Weak

Screening for prostate cancer using serum PSA has been shown to produce small reductions in prostate cancer-related deaths but at the expense of a high risk for possible overdiagnosis or overtreatment [81,82]. When combined with results from other tests such as digital rectal examination (DRE), the diagnostic yield of PSA is further enhanced [83]. However, it has been difficult to identify a particular PSA cutoff level that achieves maximum specificity and sensitivity in detecting clinically significant prostate cancer cases [84]. In these cases, confirmatory testing using prostate biopsy is desired. The actual benefits and harms of performing biopsy following an elevated PSA in asymptomatic patients with normal DRE findings needs to be determined.

Evidence to Decision

Benefit and Harm

There were no studies that directly compared prostate biopsy and watchful waiting for healthy men with elevated PSA and normal DRE findings. Indirect evidence from two studies [85,86] on the benefits of prostate biopsy was found. There were significantly more prostate cancer cases detected in patients who received a biopsy (44.7% vs. 17.3%; RR 2.59 [95% CI 2.25, 2.97], P <.001) [85] (Table 15). At least 7% with positive biopsy results yielded advanced-stage prostate cancer. In the cohort study that involved older men, a higher rate of prostate cancer cases was documented (5220/8313 or 63%) in those who had biopsy, however, data on cancer cases in the no biopsy group are not available [86]. Biopsy was associated with a significantly lower prostate cancer-related death (1.7% vs. 8.6% in the no-biopsy group; RR: 0.20 [95% CI 0.11, 0.34], P <.001) in the CAP trial [85]. Likewise, prostate-cancer-related deaths were significantly lower in the group who did not receive biopsy (0.07% vs 3.6%; RR 54.7 [95% CI 29.8, 100.5]) in the cohort study [86].

Biopsy rates in men with elevated PSA were 85% [85], 86% [87], 41% [88], and 33% [86]. In the RCTs, 60.6% to 75.8% of biopsies were negative for cancer. In contrast, the cohort study demonstrated a lesser proportion of non-diagnostic biopsies at 37.2% [81]. Overdiagnosis refers to prostate cancer cases detected through PSA screening that would not have been diagnosed within the patient's lifetime. This is considered harmful because it entails prescribing treatments that would lack benefit (since it would not change the patient's prognosis) and increase cost unnecessarily. Using the excess incidence method,

the estimated percentage of overdiagnosed prostate cancers ranged from 20.7% [88] to 50.4% [87]. However, the limited follow-up period in the 2 RCTs may exaggerate overdiagnosis estimates [81]. No increase in mortality was associated with biopsy [89,90]. In the PLCO trial (n=4861), complications were reported in 2.0% of patients or about 20.2 complications per 1000 biopsies (mostly infections, bleeding, or urinary difficulties) [91]. A higher proportion of patients (5.6% of 8313) in the Veterans cohort study experienced similar adverse effects [86]. Post-biopsy hospitalization ranged from 0.5% to 1.6% based on 1 RCT and 2 cohort studies [86,89,92]. The reported frequency of moderate or severe hematospermia, pain, or fevers within 1 week from biopsy was 20.0%, 5.7%, 4.0% respectively [89,90,93]. Men with normal biopsy results following an abnormal PSA screen showed increased prostate cancer-specific worry up to 1 year after biopsy but no increase in depression or trait anxiety [93-96].

The overall certainty of evidence for all outcomes was very low due to indirectness, inconsistency, and risk of bias.

Other Considerations

Cost

The cost of ultrasound-guided biopsy ranges from Php 1,650.00.00 (OPD) to Php 2,639.00 (ICU) based on one DOH hospital [97].

Other Guidelines

ESMO recommended doing multi-parametric magnetic resonance imaging (mpMRI) before prostate biopsy and confirming the indication for biopsy through prostate cancer risk calculators in men with elevated PSA. Transperineal biopsies are recommended over transrectal ultrasound-guided biopsies [98]. NCCN recommended repeat testing every 1-2 years for 45-75- year old men with PSA levels of 1-3 ng/mL and normal DRE results. For >75-year old men with PSA levels of <4 ng/mL, normal DRE, and no other indications for biopsy, repeat PSA testing is recommended at 1-4 year intervals. Biopsy is considered after completion of further tests which includes repeat PSA, abnormal DRE, workup for benign disease, mpMRI, and biomarkers that improve specificity [99].

Consensus Issues

For patients with normal digital rectal exam with elevated PSA and no known cause for its elevation, the panel suggested that a multiparametric MRI would be preferred. This contrast imaging delineates nodules in the prostate and classifies their likelihood of malignancy, helping decide when to proceed to a biopsy. It improves the ability to detect clinically significant prostate cancer cases and reduce overdiagnosis. However, the direct cost of the procedure is high and availability of the machine and trained staff to do the procedure is limited, therefore, widespread use is not feasible at the current time.

Another issue put forth was that the sensitivity of PSA testing for cancer detection depends on the cut-off level, 67% for cut-off >10 ng/mL and 30-35% for 4-10 ng/mL. Common causes of a rise in PSA levels other than prostate cancer include benign prostatic hypertrophy, prostatitis, urinary tract infection, high parathyroid hormone levels, prostate injury or surgery, and ejaculation.

Moreover, aside from the PSA level, the risk for development of prostate cancer varies based on the patient's age, family history, and frequency or trend in PSA elevation. PSUO recommended checking PSA levels among patients aged 50 and above or among those aged 40 and above for patients with a family history of prostate cancer.

In local clinical practice, biopsy is usually not done immediately given a single elevated PSA and normal DRE. Watchful waiting is usually done wherein PSA monitoring is done every 3 or 6 months and recommending a biopsy when there is a significant rise in PSA (PSA velocity or doubling time). However, it is possible for a "single elevated PSA value" especially if at very high levels to truly indicate a high likelihood of malignancy. However, there is as yet no consensus on what this "high level" should be. This caution was mentioned so as not to mislead general practitioners and other non-specialists who may see a patient with a single PSA value which is very high and not advise proceeding with biopsy.

Table 15. Summary of outcomes for Key Question 9

OUTCOME	NO. OF INCLUDED OBSERVATIONAL STUDIES	EFFECT ESTIMATE	CoE
Prostate cancer detection	2	50-69 years old: Significantly higher prostate cancer detection in biopsy (44.7% vs. 17.3%; RR 2.59 [95% CI 2.25, 2.97], *P* < .001). At least 7% (164/2249) positive biopsy results yielded advanced-stage prostate cancer. 75 years old +: Higher PCa detection with biopsy (5220/8313 or 63%). However, data on cancer cases in the no biopsy group are not available.	Very low
Prostate cancer-related deaths	2	50-69 years old: Biopsy had lower prostate cancer deaths (1.7% vs. 8.6% in the no-biopsy group; RR 0.20 [95% CI 0.11, 0.34], *P* < .001). 75 years old +: PCA deaths lower in the non-biopsy (0.07% vs 3.6%; RR 54.7 [95% CI 29.8, 100.5]).	Very low
Non-diagnostic biopsies	4	In the RCTs, 60.6% to 75.8% of biopsies were negative for cancer (CAP-60.6%, PLCO-67.7%, ERSPC-75.8%). In contrast, the cohort study demonstrated a lesser proportion of non-diagnostic biopsies at 37.2%.	Very low
Overdiagnosis	2	Estimated percentage of overdiagnosed prostate cancers ranged from 20.7% (PLCO) to 50.4% (ERSPC)	Very low
Biopsy-related complications	5	Biopsy-related mortality: None Complications: 2% (20.2 per 1000 biopsies); mostly infections, bleeding, difficulty urinating; higher in elderly (5.6%) Post-biopsy hospitalization: 0.5-1.6% Hematospermia: 20% Pain: 5.7% Fevers: 4.0%	Very low
Psychological harms	4	Men with normal biopsy results following an abnormal PSA screen showed increased prostate cancer-specific worry up to 1 year after biopsy but no increase in depression or trait anxiety [Brindle 2006; Fowler 2006; Katz 2007; McNaughton Collins 2004].	Very low

CI: confidence interval
CoE: Certainty of Evidence
PSA: prostate-specific antigen

Use of PSMA PET/CT versus conventional imaging for patients with biochemical recurrence of prostate cancer after local therapy

Recommendation

10. Among patients with biochemical recurrence of prostate cancer after local therapy, there is insufficient evidence to suggest the use of PSMA PET/CT over conventional imaging
Certainty of Evidence: Very low
Strength of Recommendation: None

Biochemical recurrence (BCR), a rise in the prostate specific antigen (PSA) after prostatectomy, occurs in about 20 to 40% of patients with prostate cancer after radical prostatectomy [100]. Serum PSA values of 0.4 ng/ml were associated with high risk for metastasis and cancer-related mortality [101]. It is defined as a serum PSA ≥0.2 ng/mL or a PSA rise of 2 ng/mL or more above the nadir PSA [102,103]. Around 30% of these patients would develop metastasis [104].

One of the goals of diagnostic evaluation is to detect pelvic involvement or bone metastasis to guide treatment. Conventional imaging, such as CT scan, MRI and bone scan, is used for this purpose. However, these imaging are said to be limited, especially with PSA <10ng/ml. Next-generation imaging (NGI) such as prostate specific membrane antigen positron emission tomography CT scan (PSMA PET/CT) are being utilized for biochemically-recurrent prostate cancer.

Evidence to Decision

Benefit and Harm

There were no published trials found that evaluated the use of PSMA PET/CT on overall survival, progression-free survival, and QOL among patients with biochemical recurrent (BCR) prostate cancer. Four systematic reviews (n=1580) and 1 RCT that evaluated the impact of PSMA/PET CT on the management of patients with biochemical recurrent prostate cancer and diagnostic performance of PSMA PET/CT compared to conventional imaging such as CT scan and bone scan in detecting local recurrence and metastasis were found instead (Table 16).

There is an overall change in the management in 61% (95% CI: 55 to 68%) of BCR patients. Management change mostly happened among those with serum PSA 0.5 to <1ng/ml. With the use of PSMA PET, the proportion of patients who received targeted/localized therapy, EBRT for the prostatic bed (with or without pelvic nodes) was reduced from 75.7% (356/470) to 55.2% (264/478). On the other hand, patients who received SRT and simultaneous integrated boost (SIB) increased to 18.4% (88/478) and 11.7% (56/478), respectively. The number of patients planned for surgery increased from 9 to 26 after PSMA PET. Systemic therapy decreased from 206 to 137 patients after PSMA PET [105]. One systematic review [106] had a pooled sensitivity of 76% (95% CI: 74%, 78%) in detecting local recurrence and/or metastasis in BCR patients. There was a high inconsistency between results (I2=90.7%). The specificity based on 4 studies was 42% (95% CI 27, 58%, I2=84.2). The sensitivity of conventional

imaging (chest, abdomen, bone) was 38.3 (95% CI, 24.5%, 53.6%) and its specificity was 91.3% (95% CI 84.1, 95.9%) according to one RCT (n=302) [107]. Based on a systematic review with 5 diagnostic accuracy studies [107], PSMA has a sensitivity of 84% (95% CI 61%, 95%) and a specificity of 97% (95% CI 95, 99) in detecting lymph node metastasis. Sensitivity and specificity for lymph-node involvement of conventional imaging was 22.5% (95% CI, 10.8, 38.5%) and 96.4% (95% CI 91.0, 99%). One systematic review with 4 studies involving 318 prostate cancer patients, PSMA/CT had a sensitivity of 97% (95% CI 92, 99; I2=0.7%) and specificity of 100% (95% CI 96, 100; I2=0). On the other hand, bone scans had a sensitivity of 86% (95% CI 78, 92; I2=55.8%) and specificity 87% (95% CI 81, 92%; I2=82) [108].

Based on two prospective trials, 88 patients underwent PSMA PET/CT. None of the patients reported any immediate and late adverse events [109]. Certainty of evidence for outcomes in impact of management and diagnostic performance is low to moderate. Reasons for downgrading the certainty of evidence are imprecision, inconsistency, and indirectness.

Other Considerations

Cost

No cost-effectiveness studies on PSMA PET/CT among biochemical recurrent prostate cancer patients were found. Costs of diagnostic modalities for BCR prostate cancer patients are enumerated in the table below. These costs were collected from private and government hospital on September 2021.

Table 15. Cost of diagnostic modalities

Imaging	Price
PSMA PET/CT	PhP 144,000 – 157,391
Whole abdomen CT scan	PhP 2,600 - PhP 19,405
Bone Scan	PhP 6,000 – PhP 11,610

Other Guidelines

NCCN recommended to consider (1) bone imaging (bone scan or F-18 sodium fluoride [NaF] positron emission tomography [PET]/computed tomography [CT]); (2) chest CT; (3) abdominopelvic CT or magnetic resonance imaging (MRI); and, (4) prostate bed biopsy (especially if imaging suggests local recurrence). In addition, C-11 choline or F-18 fluciclovine PET/CT or PET/MRI can be considered after bone scan for further evaluation when clinical suspicion of bone metastases is high. PSMA PET/CT can be considered as an alternative to standard imaging in detecting bone and soft tissue metastasis [110]. ASCO recommended using NGI such as PSMA PET/CT only after negative conventional imaging and if salvage therapy is being considered [111]. Among men with PSA relapse following radical prostatectomy, EAU recommended considering bone scan and abdominopelvic CT scans only for men who have a high baseline PSA (>10ng/ml) or high PSA kinetics or in those with symptomatic bone disease. For men with a biochemical recurrence after RT, histologic proof of local recurrence is necessary before treating the patient. Multiparametric MRI can be used for biopsy targeting and guidance of local salvage treatment. Detection of local recurrence is also feasible with choline and acetate PET/CT [112].

Consensus Issues

Imaging studies are not exclusively applied to diagnose prostate cancer but also to evaluate treatment response. Depending on the systemic agent that is used for treatment, imaging studies may be done every 8 to 12 weeks. Among prostate cancer patients, imaging studies are also done once there is a rise in PSA level.

FDG- and PSMA-PET scans are also utilized in exceptional circumstances to determine early signs of metastases prior to administration of any kind of treatment. In addition, the two modalities are also used in determining the optimal treatment approach among patients whose results of conventional imaging studies are discordant with the results of their serum PSA testing. Newest clinical trials still do not utilize PSMA or FDG-PET scans as a response evaluation tool. The equipment needed for FDG- and PSMA-PET scans are not widely available, especially in areas outside Metro Manila, hence widespread use will be difficult to achieve. In other countries, like Australia and India, the cost is lower than in the Philippines so their use is more common. Locally, conventional imaging is still used as the standard test because of its significantly lower cost compared to PET scans.

Table 16. Comparison of 68 GA- PSMA PET CT over conventional imaging in diagnosing recurrence/metastasis in biochemical recurrent prostate cancer

Sensitivity	0.76 (95% CI: 0.74,0.78)		
Specificity	0.42 (95% CI: 0.27,0.58)	**Prevalence**	**30%**

OUTCOME	NO. OF STUDIES	N	EFFECT PER 1,000 PATIENTS TESTED	COE
			pre-test probability of 30%(5)	
True positives (patients with recurrence)	22	4050	228 (222 to 234)	Low
False negatives (patients incorrectly classified as not having recurrence)			72 (66 to 78)	
True negatives (patients without recurrence)	4	758	294 (189 to 406)	Very Low
False positives (patients incorrectly classified as having recurrence)			406 (294 to 511)	

CoE: Certainty of Evidence
CI: confidence interval

Table 17. Comparison of 68 GA- PSMA PET CT and bone scan in diagnosing bone metastasis in biochemical recurrent prostate cancer

68 GA- PSMA PET CT		**Bone scan**			
Sensitivity	0.97;95% (CI: 0.92,0.99)	Sensitivity	0.86;95% CI: 0.78,0.92)	**Prevalences**	30%
Specificity	1.00;95% (CI: 0.80,1.00)	Specificity	0.87;95% CI: 0.81,0.92)		

OUTCOME	**NO OF STUDIES**	**n**	**EFFECT PER 1,000 PATIENTS TESTED**		**COE**
			pre-test probability of30%		
			68 GA- PSMA PET CT	bone scan	
True positives **(patients with bone metastasis)**	4	298	291 (276 to 297)	258 (234 to 276)	Moderate
			33 more TP in 68 GA- PSMA PET CT		
False negatives **(patients incorrectly classified as not having bone metastasis)**			9 (3 to 24)	42 (24 to 66)	
			33 fewer FN in 68 GA- PSMA PET CT		
True negatives **(patients without bone metastasis)**	4	298	700 (560 to 700)	609 (567 to 644)	Low
			91 more TN in 68 GA- PSMA PET CT		
False positives **(patients incorrectly classified as having bone metastasis)**			0 (0 to 140)	91 (56 to 133)	
			91 fewer FP in 68 GA- PSMA PET CT		

CoE: Certainty of Evidence
CI: confidence interval

Table 18. Use of 68 GA- PSMA PET CT in diagnosing lymph node involvement in biochemical recurrent prostate cancer

Sensitivity	0.84 (95% CI: 0.61,0.95)
Specificity	0.97 (95% CI: 0.95,0.99)

Prevalences 30%

OUTCOME	**NO. OF STUDIES**	**n**	**EFFECT PER 1,000 PATIENTS TESTED** pre-test probability of30%	**COE**
True positives **(patients with lymph node involvement)**	5	172	252 (183 to 285)	Very Low
False negatives **(patients incorrectly classified as not having lymph node involvement)**			48 (15 to 117)	
True negatives **(patients without lymph node involvement)**	5	172	679 (665 to 693)	Low
False positives **(patients incorrectly classified as having lymph node involvement)**			21 (7 to 35)	

CoE: Certainty of Evidence
CI: confidence interval

CHAPTER 4. APPLICABILITY ISSUES

Several issues related to the equity, feasibility, and availability of the interventions that were included in this guideline may influence the implementation of the recommendations at a national level. The high direct cost of some medicines mentioned in the guideline may promote greater health inequity. Newer radiotherapy modalities that are associated with fewer adverse events are significantly more expensive and available in fewer medical centers and this may also worsen health inequity. In remote areas of the country, even older radiotherapy facilities are not available and patients need to travel to urban centers to avail of this treatment. Results of the follow-up rate in the clinical trials included in the review used in this guideline may not reflect the follow-up rate in the real word setting, especially in disadvantaged areas. Active efforts must be done to address the issues on cost, accessibility, feasibility, and equity to facilitate the implementation of the guideline.

CHAPTER 5. DISSEMINATION AND IMPLEMENTATION

The manuscript of this Clinical Practice Guideline underwent external review by a clinical epidemiologist and methodology expert and will further be reviewed by other stakeholders. It will be submitted to the National Practice Guideline Clearinghouse of the DOH for review, assessment, and approval. The DOH, NKTI, and the involved organizations shall also promote the use and uptake of these recommendations nationally through publications, lectures, and other forms of notifications of all possible stakeholders.

The evidence base and the final manuscript will be made available both in print and electronic media through the DOH, the NKTI, and the organizations involved in its creation.

CHAPTER 6. RESEARCH IMPLICATIONS AND UPDATING OF THE GUIDELINE

Research Implications

There were significant research gaps identified. For some of the reviewed evidence, there was imprecision, signifying the need for more clinical trials and well-designed observational studies for the assessment of long-term adverse effects of treatment. The design of future studies need to consider improving the assessment of quality of life to avoid detection bias that may occur in open-label trials.

There is scarce publication on prostate cancer among Filipinos. There is a need to describe disease presentation, response to treatment including quality of life, patient knowledge and preferences, and full economic evaluations of interventions, both diagnostic and therapeutic. These new findings will help future guideline developers in providing streamlined recommendations to provide better clinical care for patients with prostate cancer.

Updating of the Guideline

This clinical practical guideline will be updated after three to five years, as new local and global research findings become available.

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Conflicts of Interest

The following potential conflicts of interest were declared: Dr. Minerva Calimag (Associate at UST Journal of Medicine), Ms. Edilaida Garcia (Vice President of Asian Oncology Nursing Society), and Dr. Jerry Tan Chun Bing (received honorarium from Astellas for a lecture). The following panelists had no declared conflicts of interest: Dr. Gonzalo Banuelos, Dr. Michael Caampued, Dr. Nenacia Mendoza, Mr. Christopher Muñoz, Dr. Jose Vicente Prodigalidad, and Dr. Ricardo Quimbo.

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