InaJCC The Indonesian Journal of Cancer Control

Case Report

Multidisciplinary approach in prostate cancer management: Harmonizing the role of surgery, radiation, and systemic Therapy

Dimas Priantono[1], Wulyo Rajabto[1], Rahmat Cahyanur[1], Albertus Raditya Danendra[2], Edo Aditya Dwi Susanto[1], Manika Putri Kunigara[1]

e-ISSN 2797-457X
DOI: 10.52830/inajcc.v3i3.84

Received: May 29, 2024
Accepted: September 15, 2024

Authors' affiliations:
[1]Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia-Cipto Mangunkusumo National General Hospital, Jakarta, 10430, Indonesia.
[2]Faculty of Medicine Universitas Indonesia, Jakarta, 10430, Indonesia.

Corresponding author:
E-mail: dimas.priantono@gmail.com

Abstract

Background: Prostate cancer management necessitates a comprehensive multidisciplinary approach, involving specialists such as medical oncologists, urologists, pathologists, radiologist, and radiation oncologists.
Case Illustration: A 68-year-old male underwent interventions for metastatic prostate cancer. Initially diagnosed with localized disease, he received a radical prostatectomy (RP) and subsequently underwent radiation therapy (RT) along with androgen deprivation therapy (ADT). His initial diagnosis categorized him as high-risk localized prostate cancer (stage cT2cN0M0), guided by screening recommendations, leading to a histopathological diagnosis of pT2N0M0. Prognostic factors like Gleason score and PSA level informed treatment decisions. Although PSA levels initially decreased post-prostatectomy, subsequent rises necessitated further intervention.
Discussion: Early postoperative radiotherapy and adjuvant ADT demonstrated efficacy in improving patient outcomes. Metastatic screening and subsequent therapy were guided by evidence-based protocols. Despite the patient's response to treatment, bone metastasis occurred, prompting palliative external radiation and zoledronic acid therapy. After RP, RT, ADT, palliative external RT, and bisphosphonate therapy, imaging revealed no residual lesions or signs of metastasis, with a significantly decreased PSA level.
Conclusion: This case serves as a compelling example of a multidisciplinary team's involvement in maximizing patient care and treatment effectiveness for metastatic prostate cancer.

Keywords: *multidisciplinary approach, prostate cancer, radiotherapy, surgery, systemic therapy*

Abstrak

Latar belakang:
Latar Belakang: Penatalaksanaan kanker prostat memerlukan pendekatan multidisipliner yang komprehensif, melibatkan berbagai spesialis seperti onkologi medik, urologi, patologi, radiologi, dan onkologi radiasi.
Ilustrasi Kasus: Seorang laki-laki berusia 68 tahun menjalani berbagai intervensi untuk kanker prostat metastatik. Awalnya didiagnosis dengan kanker prostat lokalisata, dan pasien menjalani prostatektomi radikal (RP), kemudian dilanjutkan dengan terapi radiasi (RT) dan terapi deprivasi androgen (ADT). Diagnosis awal menunjukkan kanker prostat lokal risiko tinggi (stadium cT2cN0M0), dan berdasarkan rekomendasi skrining, terkonfirmasi secara histopatologi sebagai pT2N0M0. Faktor prognostik seperti skor Gleason dan kadar PSA menjadi dasar pengambilan keputusan terapi. Meskipun kadar PSA awalnya menurun setelah prostatektomi, namun bila terjadi peningkatan maka memerlukan intervensi tambahan.
Diskusi: Radioterapi pascaoperasi dini dan ADT adjuvan menunjukkan efikasi dalam meningkatkan keberhasilan tata laksana pasien. Skrining metastasis dan terapi selanjutnya dilakukan berdasarkan protokol berbasis bukti. Meskipun pasien menunjukkan respons terhadap terapi, akan tetapi terjadi metastasis tulang, sehingga diberikan radioterapi eksternal paliatif dan terapi asam zoledronat. Setelah diberikan RP, RT, ADT, radioterapi eksternal paliatif, dan terapi bifosfonat, tidak tampak adanya lesi residu atau tanda metastasis pada pencitraan, dengan kadar PSA yang menurun signifikan.
Kesimpulan: Kasus ini merupakan contoh nyata peran tim multidisiplin dalam mengoptimalkan tata laksana dan efektivitas terapi pada kanker prostat metastasis.

Kata kunci: *kanker prostat, pembedahan, pendekatan multidisipliner, radioterapi, terapi sistemik*

Background

Prostate cancer is a leading malignancy among men worldwide, holding the position as the second most common cancer globally and consistently ranking in the top five in many areas such as Indonesia.[1-3] The disease progresses from prostatic intraepithelial neoplasia (PIN) to invasive adenocarcinoma, influenced by proto-oncogene activation and tumor suppressor gene inhibition.[4] Common symptoms include lower urinary tract issues, erectile dysfunction, and hematuria, though some cases are identified through PSA screening, which can yield both false positives and negatives.[5]

Digital rectal examination (DRE) aids in distinguishing benign from malignant conditions[6], while histopathological testing and imaging are essential for accurate diagnosis and staging.[7] Management approaches range from active surveillance in low-risk disease[8] to aggressive treatments for advanced-stage treatments.[9,10] Bone metastasis remains a significant challenge, affecting prognosis and quality of life.[11] Multimodal treatments, combining surgery, radiation, and systemic therapies, have shown promise in controlling disease progression and improving outcomes.[12] However, identifying predictive factors and tailoring treatments to individual patients remain critical research areas.[13]

A multidisciplinary approach is crucial for the successful management of prostate cancer, encompassing every stage from detection to treatment. This collaborative strategy involves specialists from various fields, including medical oncology, urology, pathology, radiology, and radiation oncology, working together to provide comprehensive care.[14] Early detection and accurate staging are vital, requiring coordinated imaging and biopsy interpretation efforts. Risk stratification and evaluation are enhanced by the diverse expertise within the team, ensuring personalized treatment plans.

This report details a case of advanced metastatic prostate cancer treated with a multidisciplinary approach that included various intervention modalities, demonstrating the complexity and collaborative efforts required for effective management.

Case Illustration

A 68-year-old male visited the hospital for a follow-up appointment regarding his prostate cancer therapy. Thirteen years before admission, he sought help for urinary difficulty, leading to benign prostate hyperplasia (BPH) diagnosis with elevated prostate-specific antigen (PSA) levels, remaining below 10 ng/ml. Despite regular follow-ups, his symptoms worsened over eight years, prompting a prostate biopsy confirming cancer. He experienced radical prostatectomy and pelvic lymph node dissection, resulting in a decrease in PSA levels from 37.2 to 0.54 ng/mL. However, his PSA levels gradually rose again by 2020, necessitating radiation therapy (SIB IMRT) for 25 sessions, Goserelin injections every three months, and Bicalutamide, which lowered PSA levels below the detection threshold.

He is a controlled diabetic with no smoking history. His family has no cancer history, except for his sibling's breast cancer. His Eastern Cooperative Oncology Group (ECOG) performance status is 0, with a Karnofsky performance status of 100, and a body mass index (BMI) of 22.5 kg/m². The digital rectal examination reveals a palpable, mobile tumor confined within the prostate gland, involving both lobes. No tenderness or induration is appreciated in the surrounding tissue. No palpable masses or nodules elsewhere, as well as lymphadenopathies.

The histological analysis of the prostate biopsy initially revealed adenocarcinoma on both sides with a Gleason score of 4+3 (7). Pathology, imaging, and biochemical studies established the diagnosis of pT2N0M0, PSA >20 ng/mL, grade group 3 (stage IIIA) prostate cancer. After radical prostatectomy, there was a notable decrease in the PSA level, which fell significantly to 0.54 ng/mL. One year later, the PSA level gradually increased to 1.51 ng/mL until radiotherapy. A post-treatment MRI of the prostate, after RP+SIB-IMRT+ADT, showed no pathological masses or enhancements within the prostate, with no evidence of lymphadeno-pathy. PSA post-radiotherapy decreased to 1.07 ng/mL.

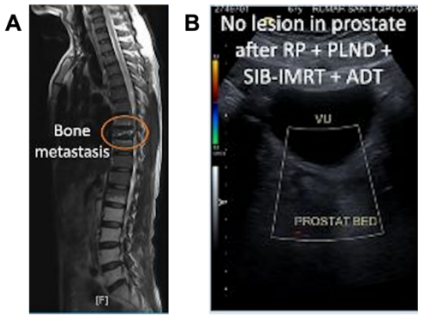

Figure 1. Imaging evaluation. Metastasis in the T9 vertebral body is shown in a contrast-enhanced MRI (A). Abdominal ultrasound examinations conducted after radical prostatectomy (RP), pelvic lymph node dissection (PLND), simultaneous-integrated boost intensity-modulated radiation therapy (SIB-IMRT), and androgen deprivation therapy (ADT) showed no focal pathological lesions in the prostate bed.

Following the patient's complaint of bone pain two months later, an anomaly was observed in a bone scan, suggesting pathological activity on the T9 vertebra's right aspect. Additionally, a thoracolumbar X-ray displayed deterioration of the T9 vertebral body on the right side, encompassing the right pedicle. A contrast-enhanced MRI confirmed metastasis in the T9 vertebral body (Figure 1A). Patient received palliative external radiation and bisphosphonate therapy while continuing ADT.

Abdominal ultrasound examinations conducted post-treatment and six months later showed no focal pathological lesions in the prostate bed or evidence of metastasis in the intra-abdominal organs (Figure 1B). Furthermore, a CT scan conducted four years after radical prostatectomy and three years into hormonal therapy and radiotherapy showed no residual lesions in the prostatic bed or signs of metastasis in the intrathoracic and intra-abdominal organs, nor any lymphadenopathy. Finally, a bone scan performed after palliative external radiotherapy, continuous monthly bisphosphonate treatment, and intermittent ADT showed no active pathological processes in the T9 vertebra, coupled with a significantly decreased PSA level of <0.008 ng/mL. PSA response to interventions is shown in Figure 2.

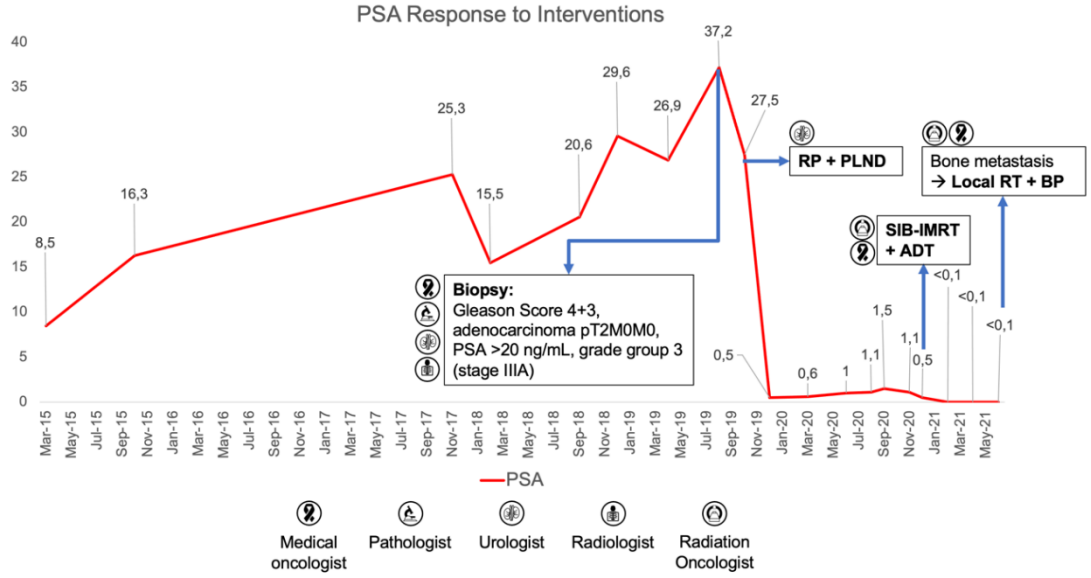

Figure 2. PSA response to interventions, highlighting the multidisciplinary approach of prostate cancer treatment. RP, radical prostatectomy; PLND, pelvic lymph node dissection; RT, radiotherapy; BP, bisphosphonate therapy; SIB-IMRT, simultaneous-integrated boost intensity-modulated radiation therapy; ADT, androgen deprivation therapy

Discussion

Prostate cancer ranks second among male cancers globally and is among the top five cancers affecting males in Indonesia.[2,3] Its sporadic occurrence accounts for about 85%, while familial cases make up 10 to 15%, and hereditary cases constitute 3-5%.[15] A family history of breast cancer is evident, which, coupled with age and a history of malignancies, poses significant risks for this patient. Prostate cancer typically manifests between the ages of 65 to 68 years.[16] The chances surge as age progresses, with a lifetime likelihood of 12.5%, escalating to 9.0% in males aged 70 years and beyond. Autopsy findings indicate that 40% of men over 60 who have not undergone screening are found to have prostate cancer, surging to 60% in those over 80.[2] Additionally, individuals with familial breast cancer exhibit a 21% elevated risk of prostate cancer and a 34% elevated chance of developing a lethal disease.[17]

During diagnosis, the patient's PSA level stood at 27.54 ng/mL, and a physical examination revealed a tumor confined within the prostate without evidence of lymphadenopathy or metastasis (stage cT2cN0M0)[18], thereby categorizing it as high-risk localized prostate cancer.[19]

The 2024 EAU Guidelines for Prostate Cancer strongly advocate for metastatic screening via PSMA-PET/CT and cross-sectional abdominopelvic imaging,

along with a bone scan, in cases of high-risk localized disease.[20] The patient underwent metastatic screening with CT abdominopelvic scan, which showed no abnormalities in the seminal vesicles, perirectal fat, or intraabdominal and pelvic organs. A bone scan was not performed due to facility limitations. Combined with histopathological studies, the initial pathological diagnosis of the patient is pT2N0M0.

Prognostic factors for this patient include Gleason score, age >60 years, tumor stage, and PSA level. A Gleason score of 4+3 is linked with a heightened risk of mortality in overall survival and cancer-specific survival when compared to a score of 3+4.[21] Using the life expectancy estimation tool recommended by the NCCN guidelines, this patient has a 77% chance of survival in 10 years and a 57% chance in 15 years if untreated.[22]

Radical prostatectomy (RP) with pelvic lymph node dissection (PLND) was selected given the patient's symptomatic presentation and favorable life expectancy.[10,23] According to the NCCN guidelines, radical prostatectomy is advised for localized disease in individuals with a projected lifespan of at least 10 years, provided that their tumor can be fully removed surgically and they do not have significant comorbidities that would make surgery inappropriate.[10] The limited PLND involved dissection of the obturator lymph nodes (left and right) and the external iliac (right) nodes. Limited PLND is preferred over extended PLND because, despite the higher detection rate of positive lymph nodes with extended PLND, it does not enhance the rate of biochemical recurrence-free survival and is linked to a greater likelihood of complications, notably lymphocele.[24,25]

The patient's likelihood of progression-free status following radical prostatectomy stands at 18% over 5 years and 10% over 10 years. The probability of remaining recurrence-free after surgery is 74% in 2 years, 52% in 5 years, 43% in 7 years, and 35% in 10 years. The 15-year prostate cancer-specific survival is 92%.[26]

Although RP+PLND reduced PSA levels from 37.2 to 0.54 ng/mL, PSA remained detectable and gradually rose again months later, which is considered a post-RP adverse feature. In principle, radical prostatectomy should result in a PSA level that cannot be detected within 21-30 days after surgery, given the 3.15-day half-life of PSA.[27] If PSA levels fail to drop to undetectable levels after RP, it's termed PSA persistence, which significantly raises the risks of cancer-related death, biochemical recurrence, and disease recurrence.[28] Given the patient's short PSA doubling time of 5.7 months and extended life expectancy, adjuvant therapy was initiated, comprising EBRT + intermittent ADT. Intermittent ADT was preferred over continuous ADT due to its potential for comparable survival outcomes with superior quality-of-life benefits.[29-31] The patient concurrently received Goserelin (a luteinizing hormone-releasing hormone [LHRH] agonist) injections every three months for one year and Bicalutamide (a first-generation antiandrogen), alongside SIB-IMRT for 25 sessions.

Adjuvant radiation therapy following RP extends the duration of biochemical progression-free survival, metastasis-free survival, and overall survival compared to simply observing the patient's condition, as demonstrated in several key randomized clinical trials (RCTs).[32] However, early postoperative radiotherapy is preferred over ART post-RP to reduce overtreatment and risk of toxicity, as there was no notable disparity in results between the two approaches in a meta-analysis.[33] In this patient, early postoperative radiotherapy was chosen over ART, with radiotherapy initiated only after one year of observation confirming a continuous increase in PSA following RP, rather than administering radiotherapy immediately after RP as in ART.

Adding ADT to radiotherapy after radical prostatectomy significantly improves patient outcomes. Two RCTs demonstrated that adding 4-6 months of ADT, either comprising LHRH agonist alone or combined with an antiandrogen, to radiotherapy after radical prostatectomy significantly improves 5-year biochemical or clinical progression rates and freedom from progression.[34,35] Comparison between RP alone versus RP combined with adjuvant ADT reveals a statistically significant improvement in 10-year cancer-specific survival (CSS) rates in the RP + ADT group (94% vs 87%), highlighting the potential benefits of adjuvant hormonal therapy in enhancing long-term outcomes.[36] Additionally, ADT and radiation therapy (RT) combination demonstrates superior metastases-free survival compared to ADT monotherapy.[37] Notably, the integration of RP, RT, and ADT yields favorable outcomes across multiple prognostic indicators observed within the initial five years post-treatment, including biochemical relapse-free survival (90.5%), metastases-free survival (95.5%), disease-specific survival (100%), and overall survival (90.6%) rates.[38]

After radiation therapy, four rounds of goserelin injections, and bicalutamide treatment, the patient's PSA level dropped below the detection threshold (<0.008 ng/mL). A decrease in PSA levels following ADT indicates a response to endocrine therapy and suggests continued sensitivity to androgens. However, two months later, the patient reported experiencing mild pain in the lower right back region. Subsequent imaging studies, including a bone scan, thoracolumbar X-ray, and contrast-enhanced MRI, confirmed the presence of metastasis in the T9 vertebral body. Approximately 85% of prostate cancer cases are initially localized, yet nearly 40% advance to metastatic disease, with over 90% of advanced cases involving bone metastases.[39]

Therapy for M1 prostate cancer is divided into treatment for M1 castration-sensitive and castration-resistant prostate cancer.[10] Following ADT, the patient's testosterone level was assessed, revealing a measurement of 16.1 nmol/L, indicating the recovery of testicular function. Combined with the patient's PSA response to previous ADT treatment, this categorizes prostate cancer as castration-sensitive (CSPC). The next step involves determining whether the cancer is of high or low volume. According to CHAARTED criteria, this patient has low-volume disease. Standard treatment for low-volume metachronous metastases typically involves ADT combined with one of the preferred regimens: Abiraterone, apalutamide, or enzalutamide.[10] However, these three medications were not listed in the national health insurance formulary at treatment time.[40] Additionally, the patient underwent EBRT, which has demonstrated efficacy in increasing overall survival, especially in patients with a low metastasis burden.[41] EBRT may be applied to bone metastases, particularly in weight-bearing bones or when a patient exhibits symptoms, both of which apply to this patient's case. If EBRT is administered with ADT, one option for ADT includes LHRH agonist either alone or given concurrently with abiraterone or docetaxel.[10] The patient received intermittent ADT (goserelin), with reintroduction of ADT if PSA levels rose above 20 ng/mL or exceeded 10 ng/mL with accompanying symptoms.[42] Bicalutamide was administered concurrently with goserelin to prevent initial testosterone flare in weight-bearing bone metastases.[43] Adding bicalutamide to LHRH agonist therapy also leads to a 22% decrease in the risk of death (P=0.0498), significantly improves overall survival rates (75.3% vs 63.4%), and markedly increases the proportion of patients accomplishing PSA nadir concentrations ≤1 ng/mL (81.4% vs 33.7%; P<0.001), while also prolonging PSA progression-free survival compared to LHRH agonist monotherapy.[44,45] Docetaxel was not prescribed due to insufficient evidence supporting its efficacy in patients with metachronous, low-volume disease.[46]

ADT poses a risk of bone loss[47,48], particularly concerning in bone metastatic prostate cancer due to elevated fracture risk. While bone antiresorptive therapy isn't indicated for reducing symptomatic skeletal-related events (SREs) and does not signifycantly increase survival in CSPC[49,50], it's recommended for managing heightened fracture risk.[10] According to the Fracture Risk Assessment Tool (FRAX; https://www.fraxplus.org/calculation-tool/), this patient has a 3.0% probability of experiencing major osteoporotic events and a 1.5% probability of hip fracture over the next ten years. Considering the fracture risk alongside the patient's bone metastasis, continuous monthly zoledronic acid was administered. In castration-resistant prostate cancer (CRPC), denosumab demonstrates superior efficacy in halting SREs compared to zoledronic acid. However, it is associated with a higher incidence of hypocalcemia and osteonecrosis of the jaw.[51] There are no direct comparative studies of bone antiresorptive drugs in metastatic castration-sensitive prostate cancer (CSPC).

Zoledronic acid is associated with hypocalcemia[52] and may worsen kidney function in patients with mild to moderate kidney disease (defined as baseline CrCl 30-60 mL/min).[53] Calcium ion and blood as well as kidney function were checked before each zoledronic acid administration for dose adjustment. The patient underwent follow-up every 1-2 months, including PSA and testosterone level checks, assessment of ADT side effects, and laboratory tests including complete peripheral blood count, serum urea and creatinine, lipid profile, blood glucose, and calcium levels. Thrombosis risk assessment was also conducted. Routine thromboprophylaxis for outpatients receiving systemic therapy for cancer is not recommended.[54]

Conclusion

This case exemplifies the efficacy of a multidisciplinary team approach in managing metastatic prostate cancer, highlighting the critical roles of urologists, pathologists, radiologists, radiation oncologists, and medical oncologists from diagnosis through ongoing treatment. The collaborative efforts of these specialists were pivotal to the successful management and

improved outcomes of the patient. Additionally, this case underscores the significance of timely identification of prostate cancer, particularly during the follow-up of BPH, to enhance early intervention and treatment effectiveness.

Acknowledgements

None.

Conflict of Interests

The authors declare no conflicts of interest.

References

1. Giona S. The Epidemiology of Prostate Cancer. In: Bott SRJ, Ng KL, editors. Prostate Cancer [Internet]. Brisbane (AU): Exon Publications; 2021 May 27. Chapter 1. Available from: https://www.ncbi.nlm.nih.gov/ books/ NBK571326/ doi: 10.36255/exonpublications. Prostate-cancer.epidemiology.2021
2. Bergengren O, Pekala KR, Matsoukas K, Fainberg J, Mungovan SF, Bratt O, et al. 2022 Update on Prostate Cancer Epidemiology and Risk Factors-A Systematic Review. Eur Urol. 2023 Aug;84(2):191-206. doi: 10.1016/j.eururo.2023.04.021.
3. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, et al. Global Cancer Observatory: Cancer Today [Internet]. Lyon, France: International Agency for Research on Cancer. 2024 [accessed May 20]. Available from: https://gco.iarc.who.int/today
4. Rybak AP, Bristow RG, Kapoor A. Prostate cancer stem cells: deciphering the origins and pathways involved in prostate tumorigenesis and aggression. Oncotarget. 2015 Feb 10;6(4):1900-19. doi: 10.18632/ oncotarget.2953.
5. Merriel SWD, Funston G, Hamilton W. Prostate Cancer in Primary Care. Adv Ther. 2018 Sep;35(9):1285-1294. doi: 10.1007/s12325-018-0766-1.
6. Jones D, Friend C, Dreher A, Allgar V, Macleod U. The diagnostic test accuracy of rectal examination for prostate cancer diagnosis in symptomatic patients: a systematic review. BMC Fam Pract. 2018 Jun 2;19(1):79. doi: 10.1186/s12875-018-0765-y.
7. Sekhoacha M, Riet K, Motloung P, Gumenku L, Adegoke A, Mashele S. Prostate Cancer Review: Genetics, Diagnosis, Treatment Options, and Alternative Approaches. Molecules. 2022 Sep 5;27(17):5730. doi: 10.3390/molecules27175730.
8. Kinsella N, Helleman J, Bruinsma S, Carlsson S, Cahill D, Brown C, Van Hemelrijck M. Active surveillance for prostate cancer: a systematic review of contemporary worldwide practices. Transl Androl Urol. 2018 Feb;7(1):83-97. doi: 10.21037/tau.2017.12.24.
9. Faiena I, Kim IY, Jang TL. Multimodal treatments for advanced prostate cancer. Oncotarget. 2019 Jan 8;10(3):255-256. doi: 10.18632/oncotarget.26525.
10. National Comprehensive Cancer Network (NCCN) Guidelines Prostate Cancer Version 4.2024. 2024 May 17 [accessed 2024 May 17]. Available from: https://www. nccn. org/professionals/physician_gls/pdf/prostate.pdf
11. Baldessari C, Pipitone S, Molinaro E, Cerma K, Fanelli M, Nasso C, Oltrecolli M, Pirola M, D'Agostino E, Pugliese G, Cerri S, Vitale MG, Madeo B, Dominici M, Sabbatini R. Bone Metastases and Health in Prostate Cancer: From Pathophysiology to Clinical Implications. Cancers (Basel). 2023 Feb 28;15(5):1518. doi: 10.3390/cancers15051518.
12. Shams M, Abdallah S, Alsadoun L, Hamid YH, Gasim R, Hassan A. Oncological Horizons: The Synergy of Medical and Surgical Innovations in Cancer Treatment. Cureus. 2023 Nov 22;15(11):e49249. doi: 10.7759/cureus.49249.
13. Hamid AA, Sweeney CJ, Hovens C, Corcoran N, Azad AA. Precision medicine for prostate cancer: An international perspective. Urol Oncol. 2024 Apr 12:S1078-1439(24)00334-X. doi: 10.1016/j.urolonc.2024.02.004.
14. Zhu S, Chen J, Ni Y, Zhang H, Liu Z, Shen P, et al. Dynamic multidisciplinary team discussions can improve the prognosis of metastatic castration-resistant prostate cancer patients. Prostate. 2021 Aug;81(11):721-727. doi: 10.1002/pros.24167.
15. Ni Raghallaigh H, Eeles R. Genetic predisposition to prostate cancer: an update. Fam Cancer. 2022 Jan;21(1):101-114. doi: 10.1007/s10689-021-00227-3.
16. Chin HW, Kim J, Rasp G, Hristov B. Prostate Cancer in Seniors: Part 1: Epidemiology, Pathology, and Screening. Fed Pract. 2015 May;32(Suppl 4):41S-44S. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6375450/
17. Barber L, Gerke T, Markt SC, Peisch SF, Wilson KM, Ahearn T, Giovannucci E, Parmigiani G, Mucci LA. Family History of Breast or Prostate Cancer and Prostate Cancer Risk. Clin Cancer Res. 2018 Dec 1;24(23):5910-5917. doi: 10.1158/1078-0432.CCR-18-0370.
18. Buyyounouski MK, Choyke PL, McKenney JK, Sartor O, Sandler HM, Amin MB, Kattan MW, Lin DW. Prostate cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017 May 6;67(3):245-253. doi: 10.3322/caac.21391.
19. Parker C, Castro E, Fizazi K, Heidenreich A, Ost P, Procopio G, Tombal B, Gillessen S; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020 Sep;31(9): 1119-1134. doi: 10.1016/j.annonc.2020.06.011.
20. EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer. Edn. presented at the EAU Annual Congress Paris April 2024. European Association of Urology 2024. Available from: https://uroweb.org/guidelines/prostate-cancer
21. Zhu X, Gou X, Zhou M. Nomograms Predict Survival Advantages of Gleason Score 3+4 Over 4+3 for Prostate Cancer: A SEER-Based Study. Front Oncol. 2019 Jul 16;9:646. doi: 10.3389/fonc.2019.00646.
22. Pre-Radical Prostatectomy. Memorial Sloan Kettering Cancer Center Nomogram. 2024 [accessed 2024 May 20]. Available from: https://www.mskcc.org/nomograms/ prostate/pre_op
23. Vernooij RW, Lancee M, Cleves A, Dahm P, Bangma CH, Aben KK. Radical prostatectomy versus deferred

treatment for localised prostate cancer. Cochrane Database Syst Rev. 2020 Jun 4;6(6):CD006590. doi: 10.1002/14651858.CD006590.pub3.
24. Fossati N, Willemse PPM, Van den Broeck T, et al. The benefits and harms of different extents of lymph node dissection during radical prostatectomy for prostate cancer: A systematic review. Eur Urol 2017;72:84-109. doi: 10.1016/j.eururo.2016.12.003
25. Zhang X, Zhang G, Wang J, Bi J. Different lymph node dissection ranges during radical prostatectomy for patients with prostate cancer: a systematic review and network meta-analysis. World J Surg Oncol. 2023 Mar 6;21(1):80. doi: 10.1186/s12957-023-02932-y.
26. Post-Radical Prostatectomy. Memorial Sloan Kettering Cancer Center Nomogram. 2024 [accessed 2024 May 20]. Available from: https://www.mskcc.org/ nomograms/ prostate/post_op
27. Kim JK, Jeong CW, Ku JH, Kim HH, Kwak C. Prostate specific antigen (PSA) persistence 6 weeks after radical prostatectomy and pelvic lymph node dissection as predictive factor of radiographic progression in node-positive prostate cancer patients. J Cancer. 2019 May 21;10(10):2237-2242. doi: 10.7150/jca.29714.
28. Kimura S, Urabe F, Sasaki H, Kimura T, Miki K, Egawa S. Prognostic Significance of Prostate-Specific Antigen Persistence after Radical Prostatectomy: A Systematic Review and Meta-Analysis. Cancers (Basel). 2021 Feb 24;13(5):948. doi: 10.3390/cancers13050948.
29. Crook JM, O'Callaghan CJ, Duncan G, et al. Intermittent androgen suppression for rising PSA level after radiotherapy. N Engl J Med 2012;367:895-903. doi: 10.1056/NEJMoa1201546
30. Schulman C, Cornel E, Matveev V, et al. Intermittent Versus Continuous Androgen Deprivation Therapy in Patients with Relapsing or Locally Advanced Prostate Cancer: A Phase 3b Randomised Study (ICELAND). Eur Urol. 2016;69:720-727. doi: 10.1016/j.eururo. 2015.10.007
31. Dong Z, Wang H, Xu M, et al. Intermittent hormone therapy versus continuous hormone therapy for locally advanced prostate cancer: a metaanalysis. Aging Male. 2015;18:233-237. doi: 10.3109/ 13685538. 2015. 1065245
32. Paz-Manrique R, Morton G, Vera FQ, Paz-Manrique S, Espinoza-Briones A, Deza CM. Radiation therapy after radical surgery in prostate cancer. Ecancermedical-science. 2023 Jun 27;17:1565. doi: 10.3332/ecancer. 2023.1565.
33. Renzulli JF 2nd, Brito J 3rd, Kim IY, Broccoli I. A meta-analysis on the use of radiotherapy after prostatectomy: adjuvant versus early salvage radiation. Prostate Int. 2022 Jun;10(2):80-84. doi: 10.1016/j.prnil.2022.01.003.
34. Carrie C, Magné N, Burban-Provost P, et al. Short-term androgen deprivation therapy combined with radiotherapy as salvage treatment after radical prostatectomy for prostate cancer (GETUG-AFU 16): a 112-month follow-up of a phase 3, randomised trial. Lancet Oncol 2019;20:1740-1749. doi: 10.1016/S1470-2045(19)30486-3
35. Pollack A, Karrison TG, Balogh AG, et al. The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): an international, multicentre, randomised phase 3 trial. Lancet 2022;399:1886-1901. doi: 10.1016/S0140-6736(21)01790-6
36. Lei JH, Liu LR, Wei Q, Yan SB, Song TR, Lin FS, Yang L, Cao DH, Yuan HC, Xue WB, Lv X, Cai YC, Zeng H, Han P. Systematic review and meta-analysis of the survival outcomes of first-line treatment options in high-risk prostate cancer. Sci Rep. 2015 Jan 12;5:7713. doi: 10.1038/srep07713.
37. Shiota M, Takamatsu D, Kimura T, Tashiro K, Matsui Y, Tomida R, et al; Japanese Urological Oncology Group. Radiotherapy plus androgen deprivation therapy for prostate-specific antigen persistence in lymph node-positive prostate cancer. Cancer Sci. 2022 Jul;113(7):2386-2396. doi: 10.1111/cas.15383
38. Omrcen T, Hrepic D, Boraska Jelavic T, Vrdoljak E. Combination of adjuvant radiotherapy and androgen deprivation therapy after radical prostatectomy in high risk prostate cancer patients - results from retrospective analysis. J BUON. 2015 Jul-Aug;20(4):1061-7.
39. Gupta N, Devgan A, Bansal I, Olsavsky TD, Li S, Abdelbaki A, Kumar Y. Usefulness of radium-223 in patients with bone metastases. Proc (Bayl Univ Med Cent). 2017 Oct;30(4):424-426. doi: 10.1080/08998280.2017.11930213.
40. Keputusan Menteri Kesehatan Republik Indonesia Nomor HK.01.07/MENKES/2197/2023 Tentang Formularium Nasional.
41. Ali A, Hoyle A, Haran ÁM, Brawley CD, Cook A, Amos C, et al. Association of Bone Metastatic Burden With Survival Benefit From Prostate Radiotherapy in Patients With Newly Diagnosed Metastatic Prostate Cancer: A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol. 2021 Apr 1;7(4):555-563. doi: 10.1001/jamaoncol.2020.7857.
42. Borque-Fernando Á, Estrada-Domínguez F, Esteban LM, Gil-Sanz MJ, Sanz G. Testosterone Recovery after Androgen Deprivation Therapy in Prostate Cancer: Building a Predictive Model. World J Mens Health. 2023 Jan;41(1):129-141. doi: 10.5534/wjmh.210178.
43. Beebe-Dimmer JL, Ruterbusch JJ, Bylsma LC, Gillezeau C, Fryzek J, Schultz NM, Flanders SC, Barlev A, Heath E, Quek RGW. Patterns of Bicalutamide Use in Prostate Cancer Treatment: A U.S. Real-World Analysis Using the SEER-Medicare Database. Adv Ther. 2018 Sep;35(9):1438-1451. doi: 10.1007/s12325-018-0738-5.
44. Akaza H, Hinotsu S, Usami M, Arai Y, Kanetake H, Naito S, Hirao Y; Study Group for the Combined Androgen Blockade Therapy of Prostate Cancer. Combined androgen blockade with bicalutamide for advanced prostate cancer: long-term follow-up of a phase 3, double-blind, randomized study for survival. Cancer. 2009 Aug 1;115(15):3437-45. doi: 10.1002/cncr.24395.
45. Yokomizo A, Morokuma F, Eto M, Shiota M, Matsuyama H, Matsumoto H, et al. Randomized controlled trial of GnRH antagonist monotherapy versus GnRH agonist plus bicalutamide (CAB) for patients with metastatic hormone-sensitive prostate cancer (mHSPC) (KYUCOG-1401). J Clin Oncol. 2022

Feb;40(6_suppl):99-99. doi:10.1200/JCO.2022.40.6_suppl.099.
46. Vale CL, Fisher DJ, Godolphin PJ, Rydzewska LH, Boher JM, Burdett S, et al; STOPCAP Collaboration. Which patients with metastatic hormone-sensitive prostate cancer benefit from docetaxel: a systematic review and meta-analysis of individual participant data from randomised trials. Lancet Oncol. 2023 Jul;24(7):783-797. doi: 10.1016/S1470-2045(23)00230-9.
47. Matsushima H, Taguchi T, Kodama S, Okubo N, Saito K, Jabłońska K, Fukumoto S, Matsumoto T. Androgen deprivation therapy-related fracture risk in prostate cancer: an insurance claims database study in Japan. J Bone Miner Metab. 2024 Mar;42(2):223-232. doi: 10.1007/s00774-024-01497-4.
48. Kim DK, Lee JY, Kim KJ, Hong N, Kim JW, Hah YS, Koo KC, Kim JH, Cho KS. Effect of Androgen-Deprivation Therapy on Bone Mineral Density in Patients with Prostate Cancer: A Systematic Review and Meta-Analysis. J Clin Med. 2019 Jan 18;8(1):113. doi: 10.3390/jcm8010113.
49. Smith MR, Halabi S, Ryan CJ, Hussain A, Vogelzang N, Stadler W, et al. Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (alliance). J Clin Oncol. 2014 Apr 10;32(11):1143-50. doi: 10.1200/JCO.2013.51.6500.
50. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al; STAMPEDE investigators. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet. 2016 Mar 19;387(10024):1163-77. doi: 10.1016/S0140-6736(15)01037-5.
51. Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet. 2011 Mar 5;377(9768):813-22. doi: 10.1016/S0140-6736(10)62344-6.
52. Al Elq AH. Symptomatic Hypocalcemia Associated with Zoledronic Acid Treatment for Osteoporosis: A Case Report. Oman Med J. 2013 Mar;28(2):e043. doi: 10.5001/omj.2013.42.
53. Perazella MA, Markowitz GS. Bisphosphonate nephrotoxicity. Kidney Int. 2008 Dec;74(11):1385-93. doi: 10.1038/ki.2008.356.
54. Khorana AA, Cohen AT, Carrier M, Meyer G, Pabinger I, Kavan P, Wells P. Prevention of venous thromboembolism in ambulatory patients with cancer. ESMO Open. 2020 Nov;5(6):e000948. doi: 10.1136/esmoopen-2020-000948.