Disease-related complications in patients with metastatic hormone-sensitive prostate cancer

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A B S T R A C T

Introduction: Prostate-specific antigen-based screening for prostate cancer reportedly does not improve cancer-specific survival. However, there remain concerns about the increasing incidence of advanced disease at initial presentation. Here, we investigated the incidences and types of complications that occur during the course of disease in patients with metastatic hormone-sensitive prostate cancer (mHSPC).

Methods: This study included 100 consecutive patients who were diagnosed with mHSPC at five hospitals from January 2016 to August 2017. Analyses were conducted using patient data extracted from a prospectively collected database, along with information about complications and readmission obtained from electronic medical records.

Results: The median patient age was 74 years and the median serum prostate-specific antigen level at diagnosis was 202.5 ng/mL. Ninety-nine patients received androgen deprivation therapy; 17 of these patients also received chemotherapy. During a mean follow-up period of 32.9 months, 41 patients reported bone pain; of these patients, 21 developed pathologic fractures and eight had cord compression. Twenty-eight patients developed retention of urine; of these patients, 10 (36%) required surgery and 11 (39%) required long-term urethral catheter use. Among 15 patients who developed ureteral obstruction, four (27%) required ureteral stenting and four (27%) required long-term nephrostomy drainage. Other complications included anaemia (41%) and deep vein thrombosis (4%). Fifty-nine (59%) patients had ≥1 unplanned hospital admission during the course of disease; 16% of such patients had >5 episodes of readmission.

Conclusion: Among patients with mHSPC, 70% experienced disease-related complications and unplanned hospital admissions, which substantially burdened both patients and the healthcare system.

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New knowledge added by this study

- Advanced prostate cancer was associated with serious disease-related complications, which required surgical interventions and unplanned hospital admissions.

Implications for clinical practice or policy

- The role of prostate-specific antigen-based screening in prostate cancer should be reconsidered.
- Early prostate cancer detection may help reduce disease-related comorbidities.
- Advances in diagnostic tools and the use of active surveillance may help to minimise the harms associated with diagnostic procedures and overtreatment of early disease.

Introduction

Prostate cancer (PCa) is the second most common cancer in men worldwide, and its incidence is rapidly increasing in Hong Kong.[1] Despite increased awareness of PCa, many patients in Hong Kong are diagnosed with advanced disease involving metastasis, which does not respond to curative treatment. Previously, there was considerable interest in using serum prostate-specific antigen (PSA) for screening and early detection of PCa, with the hope that this approach would improve treatment outcomes. However, a Cochrane review showed that screening was associated with more frequent detection of localised disease, but there was no cancer-specific survival benefit; patients may even be harmed by complications associated with diagnostic and therapeutic procedures.[2] Thus, the use of PSA-based screening has declined

in the United States in the past decade.[3] Notably, a concomitant epidemiologic shift from early to advanced disease (ie, reverse stage migration) has occurred, leading to serious concerns within the urological community.[4]

The slow progression and protracted clinical course of PCa are well-known.[5] Patients with metastatic disease can survive for several years before death, which may also be caused by other medical conditions.[6] However, during the course of disease, patients may experience complications related to PCa, including skeletal-related events and urinary tract complications. These complications can threaten a patient's quality of life and lead to increased medical expenses. To our knowledge, minimal information is available regarding the course of disease (particularly complications) in patients with advanced PCa.

Here, we assessed the incidences of complications and unplanned hospital admissions among patients with metastatic hormone-sensitive PCa (mHSPC). This information may provide useful insights regarding the disease course and treatment needs of patients with mHSPC. It may also provide a more comprehensive understanding of the potential benefits of PSA-based screening in the management of patients with PCa.

轉移性激素敏感性前列腺癌患者的疾病相關併發症

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簡介：雖然基於前列腺特異性抗原的前列腺癌篩查並未證明能提高癌症特異性生存率，然而人們仍然擔心初次就診時晚期疾病的發病率會增加。在本研究中，我們調查了轉移性激素敏感性前列腺癌患者病程中併發症的發生率和類型。

方法：本研究包括2016年1月至2017年8月期間在五間本地醫院被診斷為轉移性激素敏感性前列腺癌的100名連續患者。我們分析了從前瞻性收集的數據庫中提取的患者數據以及從電子病歷獲得的併發症和再入院資料。

結果：患者的年齡中位數為74歲，診斷時的血清前列腺特異性抗原的中位水平為202.5 ng/mL。99名患者接受了雄激素剝奪治療，其中17名患者還接受了化療。在平均32.9個月的隨訪期間，41名患者報告骨痛；在這些患者中，21名出現病理性骨折，8名出現脊髓受壓。另外，28名患者出現尿瀦留；在這些患者中，10名（36%）需要接受手術，11名（39%）需要長期使用導尿管。在發生輸尿管梗阻的15名患者中，四名（27%）需要置入輸尿管支架，四名（27%）需要長期經皮腎導管引流。其他併發症包括貧血（41%）和深靜脈血栓形成（4%）。59名（59%）患者在病程中有一次或以上計劃外入院；16%的此類患者有超過五次再入院紀錄。

結論：在轉移性激素敏感性前列腺癌患者中，70%經歷了疾病相關併發症和計劃以外的住院，這給患者和醫療保健系統帶來了沉重負擔。

Methods

The Asian Prostate Cancer (A-CaP) Study, a prospective multi-nation study designed to investigate real-world clinical management of PCa in Asia, began in January 2016. Patients with a diagnosis of PCa were recruited into the study.[7,8] Clinical information was prospectively collected, including baseline patient and disease parameters, treatment received, and clinical progress. Thus far, >30 000 patients from 14 Asian countries have been recruited (based on an unpublished annual meeting report of A-CaP meeting held on 24 November 2020).

In Hong Kong, five hospitals (Alice Ho Miu Ling Nethersole Hospital, North District Hospital, Pok Oi Hospital, Prince of Wales Hospital, and Tuen Mun Hospital) formed the Hong Kong Prostate Cancer (HK-CaP) study group as part of the A-CaP project. Since 2016, all patients who presented to these hospitals (as an outpatient or inpatient) and received a diagnosis of PCa were recruited into the Hong Kong cohort, which currently includes >1000 cases of PCa (across all stages). In this study, we identified the first 100 consecutive patients with mHSPC (with no additional inclusion or exclusion criteria), then extracted their data from the HK-CaP database. Analyses were conducted using the extracted data, along with clinical information that had been retrospectively retrieved from electronic medical records.

Continuous variables are presented as medians with interquartile ranges, while categorical variables are presented as frequencies and percentages. All statistical analyses were performed using R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided P values <0.05 were considered statistically significant.

Results

Study population

From January 2016 to August 2017, 100 consecutive patients with mHSPC were included in this study. The median age was 74 years (range, 50-93) [Table]. Overall, 17% of patients had no history of chronic disease. In contrast, 55%, 25%, 10%, and 63% of patients had pre-existing hypertension, diabetes, cerebrovascular disease, and history of smoking, respectively. The median serum PSA level at diagnosis was 202.5 ng/mL (range, 0.9-6260), and 83% of patients had abnormal findings on digital rectal examination at initial presentation. Thirteen patients (13%) had a family history of PCa. Most patients presented with symptoms, including lower urinary tract symptoms (62%), haematuria (9%), and constitutional symptoms (22%). Only 7% of patients had incidental findings of an abnormal serum PSA level during wellness screening.

Most patients (95%) had histologically proven PCa; the remaining 5% of patients had a clinical diagnosis of PCa based on a high serum PSA level (219-2779 ng/mL), with or without abnormal findings on digital rectal examination. Among patients with a histological diagnosis (n=94), the proportions with International Society of Urological Pathology grades 1 to 5 were 3.2%, 7.5%, 2.2%, 19.4%, and 67.7%, respectively. Most patients had bone metastases (96%); among them, eight patients also had visceral metastases. The remaining four patients were diagnosed with non-pelvic lymph node metastases (M1a) at initial presentation (Table).

TABLE. Demographic and clinical characteristics of the prostate cancer patients in the current study (n=100)*

Parameter	
Age, y	74 (50-93)
No history of chronic disease	17 (17%)
Hypertension	55 (55%)
Diabetes	25 (25%)
Cerebrovascular disease	10 (10%)
History of smoking (active or ex-smoker)	63 (63%)
Presenting symptoms	
Lower urinary tract symptoms	62 (62%)
Haematuria	9 (9%)
Constitutional symptoms	22 (22%)
Incidental findings of abnormal serum PSA level during wellness screening	7 (7%)
Disease characteristics	
Family history of prostate cancer	13 (13%)
Abnormal findings on digital rectal examination at initial presentation	83 (83%)
Serum PSA level at diagnosis, ng/mL	202.5 (0.9-6260)
Histological diagnosis of prostate cancer available	95 (95%)
ISUP grade (n=94)	
1	3 (3.2%)
2	7 (7.5%)
3	2 (2.2%)
4	18 (19.4%)
5	64 (67.7%)
Location of metastasis	
Bone	88 (88%)
Bone and viscera	8 (8%)
Non-pelvic lymph node only	4 (4%)

Abbreviations: ISUP = International Society of Urological Pathology; PSA = prostate-specific antigen

* Data are shown as No. (%) or median (range)

Treatment received

With the exception of one patient who selected watchful waiting, all patients received androgen deprivation therapy. Initial androgen deprivation therapies included luteinising hormone-releasing hormone antagonists (46 patients, 46%), luteinising hormone-releasing hormone agonists (with short-term antiandrogen treatment during flares) [28 patients, 28%], and bilateral orchidectomy (25 patients, 25%). Seventeen patients also received upfront chemotherapy for advanced disease; no patient received upfront abiraterone.

The mean follow-up period was 32.9 months (range, 0.3-54.2). During follow-up, 59 patients developed metastatic castration-resistant prostate cancer (mCRPC). Among these patients, older-generation antiandrogens, docetaxel, abiraterone, enzalutamide, and prednisolone alone were used by 26 (44.1%), nine (15.3%), 17 (28.8%), 18 (30.5%), and five (8.5%) patients, respectively. Thirty-two patients (32%) also received palliative radiotherapy for symptom control. Seven (11.9%) patients with mCRPC used denosumab for bone protection. The median overall survival time was 3.7 years; 33 (67.3%) patients died of PCa and 16 (32.7%) patients died of other causes, and none of these causes were cardiovascular events (Fig 1).

Complications

Only 30 patients (30%) had no disease-related complications. Among the observed complications, skeletal-related events were most common: 41 patients reported bone pain during follow-up. Of these 41 patients, 35 (85%) required regular analgesics, and 12 (29%) required opioid analgesics for pain control. Approximately half of the 41 patients (ie, 20 patients, 49%) required palliative radiotherapy for bony metastases. Moreover, 21 patients developed pathologic fractures, and eight patients had cord compression.

The second most common complication was retention of urine secondary to prostatic obstruction (28 patients, 28%). Among these 28 patients, only seven (25%) were able to discontinue urethral catheter use. Of the remaining patients, 10 (36%) required endoscopic prostatic surgery and 11 (39%) required long-term urethral catheter use.

Among 15 patients who developed ureteral obstruction, four (27%) required ureteral stenting and four (27%) required long-term nephrostomy drainage. The remaining seven (47%) patients received conservative management. During follow-up, 17 patients developed gross haematuria.

Forty-one patients (41%) developed anaemia (haemoglobin level <10 g/dL); 22 of these patients (53.7%) required transfusion. Furthermore, only four of the 41 patients received chemotherapy to manage mCRPC. Therefore, most cases of anaemia were presumably the direct result of PCa. Other complications included deep vein thrombosis

(4%), psychiatric problems (adjustment disorder or depression) [4%], and suicidal ideation (1%).

Fifty-nine (59%) patients experienced ≥1 unplanned hospital admissions during the course of disease. The proportions of patients with 1-5, 6-10, and >10 unplanned hospital admission episodes were 43%, 10%, and 6%, respectively. The indications for these admissions included skeletal-related events (bone pain, fracture, and fall, 19%), urinary complications (haematuria, ureteric obstruction, and bladder outcome obstruction, 16%), and sepsis (urosepsis, pneumonia, and infection of other origin, 28%) [Fig 2]. At least half of the admissions were presumably the direct result of PCa, such as bone pain and urinary complications.

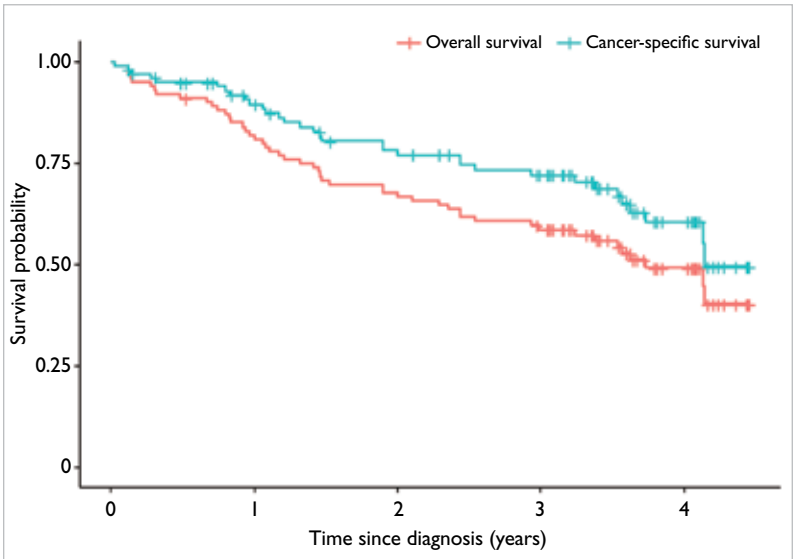

FIG 1. Overall survival and cancer-specific survival among the 100 prostate cancer patients in the current study

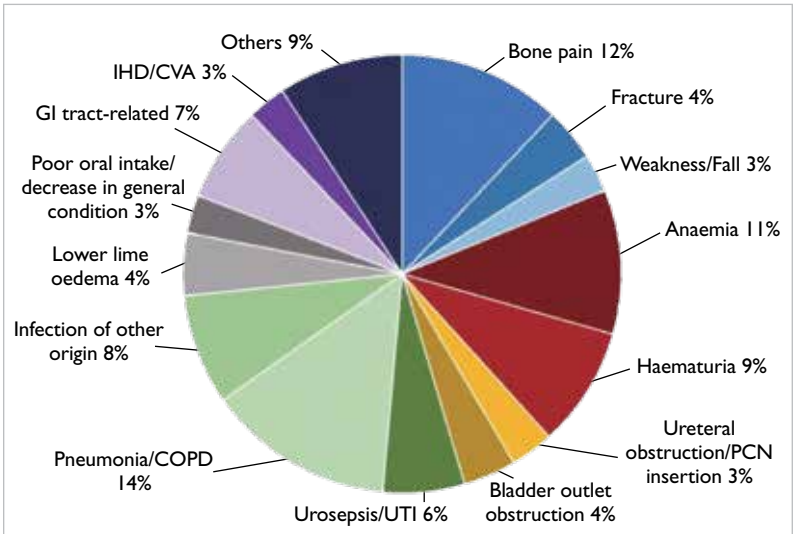

FIG 2. Indications for unplanned hospital admissions (n=59)
Abbreviations: COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; GI = gastrointestinal; IHD = ischaemic heart disease; PCN = percutaneous nephrostomy; UTI = urinary tract infection

Discussion

In this prospective observational study, over a mean follow-up period of approximately 32 months, PCa-related complications occurred in 70% of 100 patients with newly diagnosed mHSPC; around 60% of these patients had unplanned hospital admissions during the course of disease. Slightly less than half of the patients died during this study period. More than two-thirds of the patients died of PCa. Also, many of the patients experienced PCa-related complications had received various treatments for their disease and complications. These real-world data provide insights concerning the natural course of disease in patients with advanced PCa; they also suggest a need to reconsider management approaches for such patients. Additionally, these data may help to evaluate the potential benefits of PSA-based screening for PCa.

The primary purpose of disease screening involves identifying a disease in its early or asymptomatic stages, which can allow more effective treatment and support better outcomes. Consequently, disease-related mortality and complications can be minimised, while improving patient quality of life.[9] Early intervention may also help to reduce medical expenses through disease treatment at an earlier stage, rather than a later and more complex stage. Prostate cancer fulfils some of the criteria for disease screening: it is a common cancer, displays a latent disease stage, and has acceptable diagnostic tests and effective treatments.[10]

Controversies related to prostate-specific antigen–based prostate cancer screening

However, PSA-based PCa screening is among the most controversial topics in urology. In a review based on data from five randomised trials of PCa screening, no cancer-specific survival benefit was identified; moderate harm was caused by diagnostic procedures.[2] Moreover, overdiagnosis and overtreatment were common; they could cause treatment-related harm. Therefore, Chou et al[11] recommended against PSA-based screening. This recommendation led to a decline in the use of PSA testing during the past decade.[3] As expected, the overall incidence of PCa, particularly low-risk disease, has decreased in recent years.[12] Unfortunately, there has been a concomitant increase in diagnoses of advanced and higher-grade disease (ie, reverse stage migration).[4,13] Furthermore, the European Randomized Study of Screening for Prostate Cancer revealed a 30% reduction in the

relative risk of metastatic disease in the screened population, compared with the non-screened population.[14] Therefore, PSA-based screening may at least reduce the number of patients who present with metastatic disease.

Potential benefits of early cancer detection

Discussions of PSA-based screening have mainly focused on survival benefits (ie, decreases in overall and cancer-specific or all-cause mortality), as well as the harms associated with screening procedures and overtreatment of low-risk disease.[2] However, there has been minimal consideration of the potential advantages of screening in terms of preventing disease-related complications, as well as the negative effects of advanced disease on quality of life. Moreover, there has been little discussion regarding the potential financial implications of managing advanced PCa and its complications.

Rather than investigating the value of PSA-based screening, the present study was conducted to fill the gap in knowledge regarding the course of disease in patients who present with mHSPC. In our cohort, 70% of patients developed PCa-related complications (eg, bone, urinary tract, and anaemia) during the course of disease. We found that nearly 60% of patients had unplanned hospital admissions for various complications; this proportion was much greater than the observed readmission rate of 6.5% (6 of 93 patients) for localised PCa over a period of >5 years in Hong Kong.[15] Therefore, early diagnosis may be the only way to minimise the incidence of PCa-related complications in patients with mHSPC.

Treatment-related complications

In addition to PCa-related complications, cancer treatment can cause adverse effects in patients with mHSPC. Typical androgen deprivation therapy is notorious for causing cardiovascular and metabolic complications.[16-18] Treatments specifically for mCRPC, such as chemotherapy or next-generation androgen receptor targeting agents, are also associated with adverse effects such as febrile neutropenia, gastric distress, hypertension, and cardiac events.[19] Additionally, the direct and indirect costs of treatment place additional financial burdens on patients and their families (ie, 'financial toxicity'), impose a psychological burden, and adversely affect the quality of life of patients.[20] Therefore, earlier diagnosis of PCa may help patients to avoid progression to advanced or metastatic disease, thereby reducing suffering associated with advanced disease and its treatment-related complications.

Limitations

This study had some limitations. First, bone-protecting agents, which are relatively expensive, are not commonly used in Hong Kong. The absence of such agents may have led to a higher rate of skeletal-related events in our patients. Second, only 17 patients received upfront chemotherapy and no patients received upfront next-generation androgen receptor–targeting agents. Thus, we could not assess whether the use of these newer treatment approaches could minimise disease-related complications. Third, we did not collect data regarding the quality of life of patients, which would help to clarify the effects of disease-related complications on patients and their families.

In recent years, there have been many advances in PCa diagnosis and treatment. The use of new markers for PCa, such as the Prostate Health Index,[21] urinary exosomes,[22] and multiparametric magnetic resonance imaging,[23] has considerably improved diagnostic accuracy and reduced the need for prostate biopsy (ie, to rule out false-positives based on elevated PSA levels). The use of the transperineal route for prostate biopsy has also minimised prostate biopsy–related complications.[24] In addition, active surveillance for low-risk PCa has mitigated possible harms associated with overtreatment.[25] In combination, these new advances and better knowledge of the disease course will improve support for PCa screening, thereby minimising disease-related suffering.

Conclusion

In this observational study, 70% of patients with metastatic PCa at initial presentation had various PCa-related complications and many unplanned hospital admissions during the course of disease. Although there remains controversy concerning whether PSA-based PCa screening is beneficial for cancer-specific survival, the recent observation of reverse stage migration in PCa related to decreased PSA testing is problematic for PCa management. Advanced PCa may be associated with significant disease-related complications; it can also place an increased burden on the healthcare system by contributing to more unplanned hospital admissions. Thus, there is a need for more comprehensive assessment of the value of PSA-based PCa screening in terms of preventing disease-related morbidity and mortality. Advances in diagnostic tools and the use of active surveillance may help reduce the harms associated with diagnostic procedures and overtreatment of early disease.

Author contributions

Concept or design: CF Ng.
Acquisition of data: CWH Mak, SYS Chan, ML Li, CH Leung.
Analysis or interpretation of data: CWH Mak, CH Leung.
Drafting of the manuscript: CF Ng, CWH Mak.
Critical revision of the manuscript for important intellectual content: JYC Teoh, PKF Chiu, PSK Chu.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As editors of the journal, CF Ng and JYC Teoh were not involved in the peer review process. Other authors have disclosed no conflicts of interest.

Declaration

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Ethics approval

The study protocol was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (Ref No.: 2014.251) and registered in ClinicalTrials.gov (Identifier: NCT03344835). Informed patient consent has been waived by the Committee because of the observational nature of the study.

References

1. Teoh JY, Hirai HW, Ho JM, Chan FC, Tsoi KK, Ng CF. Global incidence of prostate cancer in developing and developed countries with changing age structures. PLoS One 2019;14:e0221775.
2. Ilic D, Neuberger MM, Djulbegovic M, Dahm P. Screening for prostate cancer. Cochrane Database Syst Rev 2013;(1):CD004720.
3. Fleshner K, Carlsson SV, Roobol MJ. The effect of the USPSTF PSA screening recommendation on prostate cancer incidence patterns in the USA. Nat Rev Urol 2017;14:26-37.
4. Reese AC, Wessel SR, Fisher SG, Mydlo JH. Evidence of prostate cancer "reverse stage migration" toward more advanced disease at diagnosis: data from the Pennsylvania Cancer Registry. Urol Oncol 2016;34:335.e21-8.
5. Popiolek M, Rider JR, Andrén O, et al. Natural history of early, localized prostate cancer: a final report from three decades of follow-up. Eur Urol 2013;63:428-35.
6. Tangen CM, Faulkner JR, Crawford ED, et al. Ten-year survival in patients with metastatic prostate cancer. Clin Prostate Cancer 2003;2:41-5.
7. Akaza H, Hirao Y, Kim CS, et al. Asia prostate cancer study (A-CaP Study) launch symposium. Prostate Int 2016;4:88-96.
8. Lojanapiwat B, Lee JY, Gang Z, et al. Report of the third Asian Prostate Cancer study meeting. Prostate Int 2019;7:60-7.
9. The Society of Radiographers. NHS screening programmes–purpose of the programmes. Available from: https://www.sor.org/getmedia/160c519f-7d43-4138-95f4-84e955bc2857/nhs_population_screening_2.pdf. Accessed 10 Jun 2023.
10. Wilson JM, Jungner G, World Health Organization. Public Health Papers. Principles and practice of screening for disease. World Health Organization, 1968. Available from: https://apps.who.int/iris/handle/10665/37650. Accessed 10 Jun 2023.
11. Chou R, Croswell JM, Dana T, et al. Screening for prostate cancer: a review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2011;155:762-71.
12. Jemal A, Culp MB, Ma J, Islami F, Fedewa SA. Prostate cancer incidence 5 years after US Preventive Services Task Force Recommendations against screening. J Natl Cancer Inst 2021;113:64-71.
13. Hu JC, Nguyen P, Mao J, et al. Increase in prostate cancer distant metastases at diagnosis in the United States. JAMA Oncol 2017;3:705-7.
14. Schröder FH, Hugosson J, Carlsson S, et al. Screening for prostate cancer decreases the risk of developing metastatic disease: findings from the European Randomized Study of Screening for Prostate Cancer (ERSPC). Eur Urol 2012;62:745-52.
15. Ng CF, Kong KY, Li CY, et al. Patient-reported outcomes after surgery or radiotherapy for localised prostate cancer: a retrospective study. Hong Kong Med J 2020;26:95-101.
16. Hu JR, Duncan MS, Morgans AK, et al. Cardiovascular effects of androgen deprivation therapy in prostate cancer: contemporary meta-analyses. Arterioscler Thromb Vasc Biol 2020;40:e55-64.
17. Ng CF, Chiu PK, Yee CH, Lau BS, Leung SC, Teoh JY. Effect of androgen deprivation therapy on cardiovascular function in Chinese patients with advanced prostate cancer: a prospective cohort study. Sci Rep 2020;10:18060.
18. Shore ND, Saad F, Cookson MS, et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. N Engl J Med 2020;382:2187-96.
19. Tonyali S, Haberal HB, Sogutdelen E. Toxicity, adverse events, and quality of life associated with the treatment of metastatic castration-resistant prostate cancer. Curr Urol 2017;10:169-73.
20. Rotter J, Spencer JC, Wheeler SB. Financial toxicity in advanced and metastatic cancer: overburdened and underprepared. J Oncol Pract 2019;15:e300-7.
21. Chiu PK, Ng CF, Semjonow A, et al. A multicentre evaluation of the role of the Prostate Health Index (PHI) in regions with differing prevalence of prostate cancer: adjustment of PHI reference ranges is needed for European and Asian settings. Eur Urol 2019;75:558-61.
22. Wang WW, Sorokin I, Aleksic I, et al. Expression of small noncoding RNAs in urinary exosomes classifies prostate cancer into indolent and aggressive disease. J Urol 2020;204:466-75.
23. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med 2018;378:1767-77.
24. Chiu PK, Lo KL, Teoh JY, et al. Sectoral cancer detection and tolerability of freehand transperineal prostate biopsy under local anaesthesia. Prostate Cancer Prostatic Dis 2021;24:431-8.
25. Kinsella N, Helleman J, Bruinsma S, et al. Active surveillance for prostate cancer: a systematic review of contemporary worldwide practices. Transl Androl Urol 2018;7:83-97.