

Consensus statements on the management of clinically localized prostate cancer from the Hong Kong Urological Association and the Hong Kong Society of Uro-Oncology

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Objective

To formulate consensus statements to facilitate physician management strategies for patients with clinically localized prostate cancer (PCa) in Hong Kong by jointly convening a panel of 12 experts from the two local professional organizations representing PCa specialists, who had previously established consensus statements on the management of metastatic PCa for the locality.

Methods

Through a series of meetings, the panellists discussed their clinical experience and the published evidence regarding various areas of the management of localized PCa, then drafted consensus statements. At the final meeting, each drafted statement was voted on by every panellist based on its practicability of recommendation in the locality.

Introduction

In Hong Kong, the incidence of prostate cancer (PCa) has been on a steady rise over the past several decades [1]. PCa is a common cancer and a significant cause of death in the male population of Hong Kong [2]. In recent years, there have been a number of controversies over the management of localized PCa [3,4]. To optimize the diagnostic and treatment approaches to localized PCa in Hong Kong, a local expert panel co-organized by the Hong Kong Urological Association (HKUA) and the Hong Kong Society of Uro-Oncology (HKSUO), which previously established consensus statements on the management of metastatic PCa for the territory [5], was re-convened to formulate consensus statements on the

Results

A total of 76 consensus statements were ultimately accepted and established by panel voting.

Conclusion

Derived from the recent evidence and major overseas guidelines, along with local clinical experience and practicability, the consensus statements were aimed to serve as a practical reference for physicians in Hong Kong for the management of localized PCa.

Keywords

consensus, Hong Kong, localized prostate cancer, male, #PCSM, #ProstateCancer

management of localized PCa, based on recent clinical evidence and the panellists' insights.

Methods

The panellists were listed by affiliation and specialty in a previous consensus publication [5]. They discussed the following seven major areas regarding the management of localized PCa: (1) diagnostic evaluation recommended for men with suspicious clinically localized PCa; (2) diagnostic evaluation for patients with localized PCa confirmed by biopsy; (3) parameters for treatment decisions for localized PCa; (4) risk stratification of newly diagnosed localized PCa; (5) treatment approaches to localized PCa; (6) follow-up and monitoring after definitive local treatment; and (7)

management of *de novo* pelvic nodal disease (with evidence of pelvic lymph node metastasis on presentation, but M0).

The relevant literature was searched on the PubMed database using the following keywords: ‘active surveillance’; ‘androgen deprivation’; ‘AR signalling pathway inhibitors’; ‘biomarker’; ‘biopsy’; ‘bone scan’; ‘chemotherapy’; ‘focal therapy’; ‘guideline’; ‘localized prostate cancer’; ‘magnetic resonance imaging’; ‘pelvic dissection’; ‘pelvic floor muscle training’; ‘pelvic nodal disease’; ‘penile rehabilitation’; ‘positron emission tomography (PET)’; ‘progression’; ‘radical prostatectomy’ (RP); ‘radiotherapy’ (RT); ‘recurrence’; ‘risk stratification’; ‘surgery’; ‘watchful waiting’; and ‘work-up’ [evaluation]. Only articles published between January 2005 and June 2017 were included for review.

Using a modified Delphi method [6] (Appendix S1), a series of panel meetings were held for discussions on clinical experience and available evidence, for the ultimate purpose of developing consensus statements. Based on the approach previously used to generate consensus statements [5], every panellist voted on each statement anonymously at the final meeting. A consensus statement was accepted only if $\geq 80\%$ of the panellists chose ‘accept completely’ or ‘accept with some reservation’. Full voting results for each drafted statement are included in Appendix S2.

Results

A total of 76 consensus statements were accepted and established by panel voting.

Part 1: Diagnostic Evaluation Recommended for Men with Suspicious Clinically Localized Prostate Cancer

Statement 1: ‘For men with PSA = 4–10 ng/mL (not caused by infections or urethral manipulation), a biopsy should be considered to confirm PCa, in particular among those with symptoms, an abnormal DRE result, or relevant family history. Before a biopsy is done, free/total PSA (f/t PSA) ratio or prostate health index (PHI) can be considered to aid the counselling process.’

Based on a number of large screening studies, normal PSA levels have been defined as ≤ 4 ng/mL [7]. Men with PSA levels of 4–10 ng/mL have a 22–27% chance of developing PCa, while those with PSA levels >10 ng/mL have a 67% chance [7]; therefore, in men with PSA levels of 4–10 ng/mL, it is reasonable to conduct a biopsy to diagnose PCa, given that non-cancer-related causes of elevated PSA levels, such as prostatitis and urethral manipulation, have been excluded. In particular, those with clinically suspicious symptoms of PCa or relevant family history, in addition to elevated PSA levels, should undergo a biopsy. In cases of an abnormal DRE, a follow-up biopsy should be performed, regardless of the PSA level [8].

To reduce unnecessary biopsies, f/t PSA ratio or PHI can be used to assist in the clinical judgement and counselling process. In a report by Catalona et al. [9], a lower f/t PSA ratio was associated with a higher risk of PCa, which ranged from 8% (f/t PSA ratio $>25\%$) to 56% (f/t PSA ratio $\leq 10\%$), in men with PSA levels 4–10 ng/mL. Hence, f/t PSA ratio $\leq 25\%$ can act as a cut-off point for biopsy decision-making. Regarding PHI, Ng et al. [10] found that, among Asian men with PSA levels of 4–10 ng/mL, a threshold of PHI >26.54 for performing a biopsy yielded a specificity of 49.76% (95% CI 42.8–56.7; sensitivity, 90%) in the detection of PCa.

Statement 2: ‘To detect PCa in biopsy-naïve men, a TRUS-guided systematic biopsy (10–12 cores) is recommended.’

Based on several systematic reviews [11–13], in the initial biopsy setting for overall PCa detection, targeted biopsies have no clear advantage over systematic biopsies. A similar result was found in a prospective study conducted in Hong Kong [14]. Meanwhile, there is emerging evidence that suggests the use of multiparametric (mp)MRI as a triage test before first prostate biopsy. The PROMIS study [15] showed that using mpMRI could reduce unnecessary primary biopsies by 27% and the diagnosis of clinically insignificant cancers by 5%. Subsequent TRUS biopsies guided by mpMRI could detect up to 18% more cases of clinically significant cancer compared with the standard pathway of TRUS biopsy. In the updated guideline of the National Institute for Health and Care Excellence (NICE) in the UK [16], which is in development and due to be published in April 2019, mpMRI is recommended as the first-line investigation for men with suspected clinically localized PCa, and mpMRI-guided prostate biopsy should be offered to men with a Likert score ≥ 3 .

The use of mpMRI and mpMRI-guided biopsy in the first-line setting is currently debatable, as the practice has not been consistently recommended across the literature or various guidelines. The local clinical experience using mpMRI in the biopsy-naïve setting is limited. In addition, the Likert score, suggested by NICE as a measure for performing mpMRI-guided biopsy [16], is a relatively new criterion, and one that has not been generally recognized among local physicians. Although there is increasing evidence on the role of mpMRI and fusion biopsy in improving the detection of localized PCa, their use in the first-line setting remains investigational in Hong Kong, until more data and experience are gained. In view of current local clinical experience, a TRUS-guided systematic 10–12 core biopsy remains the standard scheme for the diagnosis of PCa.

Statement 3: ‘To detect PCa in a repeat biopsy setting, mpMRI or the combination of systematic and MRI-targeted biopsies (either with cognitive guidance or mpMRI/ultrasound fusion) can be offered.’

In a study from Hong Kong [14], mpMRI showed a promising specificity for negative imaging, with no PCa detected on systematic biopsy of 11 MRI-negative patients, and the combination of systematic (12-core) and mpMRI/TRUS fusion-guided biopsies yielded a significantly higher overall cancer detection rate compared with a systematic biopsy (33.3% vs 17.6%; $P = 0.01$). Because of its high specificity, mpMRI has been recommended by clinical guidelines to confirm the diagnosis of PCa when initial biopsy results are negative [17]. With higher PCa detection rates [13], the combination of systematic and MRI-targeted biopsies is preferred to systematic biopsies alone in the repeat biopsy setting, while the targeted biopsy involved can be guided by either cognitive registration or mpMRI/TRUS fusion, because there is no significant difference in overall PCa detection rates between these two means of guidance [12]. Thus, mpMRI or the combination of systematic and MRI-targeted biopsies can be used to confirm the diagnosis of PCa in the repeat biopsy setting.

Part 2: Diagnostic Evaluation for Patients with Localized Prostate Cancer Confirmed by Biopsy

Statement 1: 'In cases of a PSA ≤ 20 ng/mL, Gleason score $\leq 3 + 4$, International Society of Urological Pathology (ISUP) grade ≥ 2 , or tumour size $\geq T2b$, mpMRI should be performed to check for the presence of extracapsular extension and pelvic status before curative treatment planning.'

Despite its low sensitivity (~58%), mpMRI is the optimal imaging tool because of its high specificity (~90%) for the detection of extracapsular extension in localized PCa [18,19], which is a poor prognostic factor associated with disease progression and decreased overall and PCa-specific survival after RP [20,21]. The high specificity of mpMRI can help reduce the unnecessary exclusion of patients from curative surgery [18,19].

Statement 2: 'In cases of a PSA > 20 ng/mL or Gleason score $\geq 4 + 3$, further imaging should be performed for metastatic staging. Whole-body prostate-specific membrane antigen (PSMA) PET-CT is preferred if resources or facilities are available. Otherwise, pelvic MRI plus bone scan is an acceptable option.'

Considering the high risk of metastatic spread in patients with PSA levels > 20 ng/mL or a Gleason score $\geq 4 + 3$, identification of metastases is crucial for determining treatment approaches. The use of PET using PSMA ligands for the detection of metastatic disease in vulnerable patients with localized PCa has been increasing. PSMA PET (using ^{68}Ga -PSMA in most studies) combined with CT has superior sensitivity and specificity in the detection of bone and nodal involvement compared with bone scan, MRI, CT and PET-CT using other tracers [22–24]; therefore, whole-body PSMA

PET-CT is a preferable imaging tool for metastatic staging in susceptible patients, although more prospective studies are warranted to evaluate the effect of the technique on treatment outcomes.

Considering cost and facility issues in some local healthcare institutions, the combination of pelvic MRI and bone scan is an acceptable alternative for metastatic staging in patients with PSA levels > 20 ng/mL or a Gleason score $\geq 4 + 3$ [25,26].

Part 3: Parameters for Treatment Decisions for Localized Prostate Cancer

Statement 1: 'Factors important for PCa treatment decision-making include: (i) life expectancy (i.e. < 10 years vs ≥ 10 years); (ii) comorbidities; (iii) performance status; (iv) ISUP grading; (v) TNM staging; (vi) Gleason score; and (vii) serum PSA level and PSA velocity.'

Life Expectancy

Nowadays, men diagnosed with early-stage PCa are expected to live for a significant period possibly because of the healthy screener effect [27]. In a population-based study in the USA [28], patients diagnosed with loco-regional PCa had higher non-cancer survival rates than the general population. Similarly, a Swedish population-based study [29] found that, compared with PCa-free men, men with low-risk PCa had reduced 10-year all-cause mortality, while men with intermediate- and high-risk PCa had increased all-cause mortality, with PCa as the most common death cause among them. Many men with PCa have a life expectancy higher than expected compared with their age- and race-matched counterparts [27]. The life expectancy of individuals with PCa should be assessed carefully based on age and comorbidity when deciding on an optimal management approach.

Comorbidities

In population-based studies [29,30], localized PCa and a higher Charlson comorbidity index score (≥ 2) were generally associated with a higher overall mortality and lower PCa-specific mortality, because such men had a significant risk of death from a competing medical hazard other than PCa. Comorbidities are worth considering to prevent overtreatment in men with localized PCa who are more threatened by non-PCa health risks [31].

Performance Status

Similarly to comorbidities, poor performance status may pose additional threats to men with localized PCa, so it is deemed relevant to guide treatment strategies between surgery, radiation and palliative hormonal therapy.

International Society of Urological Pathology Grading

The grading system of PCa established by the ISUP (Table 1) [32] has been increasingly adopted by different countries. The prognostic effect of the five grading categories has been validated in a large multi-institutional study of >20 000 RP cases and >5000 RT cases [33]. Compared with Gleason score, ISUP grading simplifies the classification of PCa, with the lowest grade being 1, as opposed to 6, which may help reduce overtreatment of PCa [33]. The ISUP grading system has been accepted by the WHO for the classification of prostate tumours [34]. The grading system is worthy of use for the pathological assessment of PCa in Hong Kong.

TNM Staging

The TNM staging is a major component in the risk stratification of PCa, and thus crucial in guiding treatment decisions. Tumour volume has been shown to be independently correlated with PSA recurrence in men undergoing RP for localized PCa [35]. Hence, it, along with other clinical variables, may serve as a prognostic factor of outcomes of RP.

Gleason Score

The Gleason score plays a crucial role in stratifying the risk of localized PCa and is also the basis of the ISUP grading system. A high Gleason score (9–10) has been shown to be associated with poor survival outcomes in patients treated with RP or RT for localized PCa [36,37].

Serum PSA and PSA Velocity

Serum PSA and its derivatives have been shown to be prognostic factors of treatment outcomes in patients with localized PCa. In a retrospective cohort study of men treated with RT for localized PCa [38], a PSA velocity >2.0 ng/mL vs ≤2.0 ng/mL during the year before diagnosis was associated with a significantly higher risk of PCa-specific death (adjusted hazard ratio [HR] 12.0, 95% CI 3.0–54.0; $P = 0.001$), suggesting that androgen deprivation therapy (ADT) in addition to RT may be considered in men with a higher PSA

Table 1 International Society of Urological Pathology grades relative to Gleason scores [32].

Gleason score	ISUP grade
2–6	1
7 (3 + 4)	2
7 (4 + 3)	3
8 (4 + 4 or 3 + 5 or 5 + 3)	4
9–10	5

ISUP, International Society of Urological Pathology.

velocity and with higher-risk disease to improve survival. A prospective study [39] found that PSA density (serum PSA level/prostate volume) was a significant determinant of PSA velocity in untreated, localized PCa, and that patients with low-risk PCa but a high PSA density (≥ 0.15 ng/mL/mL) might be more likely to benefit from immediate radical treatment rather than active surveillance.

Part 4: Risk Stratification of Newly Diagnosed Localized Prostate Cancer

Statement 1: ‘The D’Amico risk stratification of localized PCa is the basis of the subsequent statements on treatment strategies, as it was adopted in most of the published research.’

The D’Amico risk stratification [40] is a well-established system to stratify patients with localized PCa into three risk groups (Table 2), which facilitates decision-making on treatment approaches and has been widely used in the currently available literature. It has been a reference for the management of localized PCa in most cancer centres in Hong Kong; therefore, the D’Amico risk stratification of localized PCa is adopted as the basis of the subsequent statements on treatment strategies.

Statement 2: ‘It is acknowledged that the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) released their updated risk stratifications in 2017, which allow more individualized classification of patients compared with the D’Amico risk stratification; however, the subsequent consensus statements on treatment strategies are still generally applicable when referring to these updated risk stratification systems.’

The EAU and the NCCN in the USA released their respective latest guidelines on the management of localized PCa in 2017 [17,41], which include more individualized classification of patients compared with the D’Amico risk stratification. Although the consensus statements to follow on treatment strategies are primarily based on the D’Amico risk stratification, they are still generally applicable when following the 2017 guidelines. Indeed, some recommendations that were suggested recently by the EAU and the NCCN have been incorporated into the following consensus statements where applicable.

Part 5: Treatment Approaches to Localized Prostate Cancer

Watchful Waiting

Statement 1: ‘Watchful waiting should be offered to patients not eligible for local curative treatment (e.g. poor pre-morbid status) and those with a short life expectancy (<10 years), irrespective of the risk group.’

Table 2 D'Amico risk stratification of localized prostate cancer [40].

Low risk	Intermediate risk	High risk
PSA <10 ng/mL and Gleason score <7 and cT1–2a	PSA = 10–20 ng/mL or Gleason score = 7 or cT2b	PSA >20 ng/mL or Gleason score >7 or ≥cT2c

The above statement was mainly based on two randomized studies conducted in men with early PCa [42,43]. In the Scandinavian Prostate Cancer Group Study Number 4 trial [42], after 23.2 years of follow-up, compared with watchful waiting, RP was associated with significant reductions in all-cause mortality, cancer-specific mortality, and the risk of metastases among men with intermediate-risk PCa (absolute difference: 15.5, 24.2 and 19.9 percentage points, respectively). Among the low-risk group, although RP was associated with significant reductions in all-cause mortality and the risk of metastases (absolute difference: 15.6 and 10.6 percentage points, respectively), no significant reduction in cancer-specific mortality was observed (absolute difference: 3.8 percentage points). In men with high-risk PCa, there was no significant reduction in any of the three primary endpoints among those treated with RP. The Prostate Cancer Intervention Versus Observation Trial [43] found that, after 19.5 years of follow-up, RP was associated with lower all-cause mortality than was observation among men with intermediate-risk PCa (absolute difference: 14.5 percentage points), but not among those with low-risk or high-risk disease (absolute difference: 0.7 and 2.3 percentage points, respectively).

The similar results of the two trials imply that, owing to its survival benefits, RP, rather than watchful waiting, is particularly favourable for men with intermediate-risk disease who have long life expectancies. In contrast, RP may have no significant survival benefits compared with observation among men with low-risk PCa; therefore, watchful waiting may be considered before early use of radical treatment. The approach is also worth considering in men with high-risk PCa, especially those with a poor prognosis and a short life expectancy, because RP may not benefit them. In short, watchful waiting can be an option for all patients with PCa who are ineligible for local curative treatment.

Active Surveillance

Statement 1: 'Active surveillance is an option for patients with a life expectancy of >10 years and low-risk PCa, i.e. biopsy Gleason score 6, ≤2 positive biopsies, minimal biopsy core involvement (≤50% cancer per biopsy), PSA ≤10 ng/mL, and cT1–2.'

A number of prospective series [44] showed positive overall survival (OS) and disease-specific survival rates (70–90%) among men with low-risk PCa treated with active surveillance. Most of the studies, however, had a relatively short follow-up (5–10 years). In a more mature series [45], among men receiving active surveillance (25% with intermediate-risk PCa), the 10- and

15-year OS rates were 80% and 62%, respectively; the 10- and 15-year actuarial cause-specific survival rates were 98.1% and 94.3%, respectively. Another large cohort study [46] showed that OS, cancer-specific survival and metastasis-free survival rates among men with low-risk PCa under active surveillance were 93%, 99.9% and 99.4%, respectively, at 10 years and 69%, 99.9% and 99.4%, respectively, at 15 years. In the ProtecT randomized trial [47], among 2664 patients with localized PCa, the numbers of PCa-specific deaths at a median follow-up of 10 years were low, regardless of the treatment assigned (eight, five and four in the active surveillance, surgery and RT groups, respectively), with no significant difference among the groups; however, compared with active surveillance, surgery and RT were associated with lower incidences of disease progression and metastases.

Based on the above evidence, together with the EAU guidelines [17], active surveillance is an option for men with low-risk PCa who have a life expectancy of >10 years. Although there is no standard protocol for active surveillance across different international guidelines [48], regular PSA testing and biopsies are widely adopted. If active surveillance is chosen, physicians should ensure the patient's adherence to the follow-up protocol and counsel him about the potential need for further treatment in the future.

Focal Therapy

Statement 1: 'Focal therapy is not recommended in patients with localized PCa, regardless of the risk category, except in a clinical trial setting.'

In a systematic review [49], the rates of disease recurrence in patients with PCa treated with cryotherapy and those treated with high-intensity focused ultrasonography were 13.2–26% and 7.3–67.9%, respectively. At 12 months, >95% and >85% of patients demonstrated continence and sexual potency, respectively, regardless of the type of focal therapy used. Despite the positive outcomes, the clinical use of focal therapy for PCa remains controversial [50]. The main limitation of this treatment method is the difficulty in localizing the lesions in most cases; therefore, it is not recommended as a standard treatment for PCa.

Surgery

Radical prostatectomy

Statement 1: 'RP should be a treatment option for patients with localized PCa, regardless of the risk category.'

Radical prostatectomy is a standard treatment option for localized PCa, based on the survival benefits compared with watchful waiting as shown in the randomized controlled trial Scandinavian Prostate Cancer Group Study Number 4 [51,52].

Statement 2: ‘RP approaches can be robot-assisted laparoscopic, pure laparoscopic, open retropubic, or perineal, depending on the patient’s and the surgeon’s preference.’

In a systematic review that analysed two randomized trials [53], although there was no high-quality evidence to show the comparative oncological outcomes of laparoscopic radical prostatectomy (LRP) or robot-assisted radical prostatectomy (RARP) compared with open radical prostatectomy (ORP) in the treatment of PCa, all of the surgical approaches were found to have similar urinary and sexual quality-of-life-related outcomes. In comparison with ORP, LRP or RARP may be associated with a shorter hospital stay and fewer blood transfusions. In a retrospective analysis conducted in Hong Kong [54], there was no significant difference in early oncological outcomes between RARP and ORP, while RARP may lead to less blood loss and a shorter hospital stay than ORP, consistent with the conclusions of the systematic review.

A study carried out at a Chinese medical centre [55] found that, among patients with PCa who were treated with RARP, postoperative continence at 1 year and 6 months was better in those treated by the surgeons with previous LRP experience compared with those treated by a surgeon with prior ORP experience only. This implies that previous LRP experience may improve the learning curve of RARP.

Because current evidence does not show a significant difference in functional outcomes between different surgical techniques, surgeons are expected to select an approach based on their own preference, experience and patients’ acceptance.

Nerve-sparing surgery

Statement 1: ‘Nerve-sparing surgery should be offered to patients with a low risk of extracapsular disease (based on nomograms), regardless of the PCa risk category.’

According to the EAU guidelines [17], nerve-sparing surgery is recommended in patients with localized PCa who have a low risk of extracapsular disease. The practice has been adopted by local urologists in general. To assess the risk of extracapsular disease, physicians should consider the patient’s baseline erectile function and the location and extent of the tumour with reference to nomograms.

Pelvic lymph node dissection

Statement 1: ‘Pelvic lymph node dissection (PLND) is the gold standard for nodal staging in the detection of lymph node invasion (LNI) in localized PCa.’

Conventional imaging tools, such as CT and MRI, are unable to predict LNI in PCa [56,57], while the use of emerging techniques, such as PET-CT, remain investigational in this field; therefore, PLND is currently the most reliable staging method for the detection of LNI in PCa.

Statement 2: ‘Standard PLND includes removal of obturator nodes, with or without removal of external iliac nodes.’

Statement 3: ‘Extended PLND (ePLND) includes the removal of obturator, external iliac and hypogastric nodes, with or without the removal of presacral and common iliac nodes.’

When carrying out PLND, surgeons must decide on the extent based on the clinical needs of patients. Standard, or limited, PLND is restricted to the removal of obturator nodes, with the removal of external iliac nodes in some circumstances. The definition of ePLND varies in the literature, but in general, it should involve the removal of lymph nodes along the hypogastric artery [56]. Based on clinical practice, ePLND should involve the removal of obturator, external iliac and hypogastric nodes, irrespective of the removal of presacral and common iliac nodes.

Extended PLND is significantly more accurate in the detection of lymph node metastasis compared with standard PLND, which is often associated with a bias towards low rates of LNI because of insufficient nodal sampling [56,57]. Hence, ePLND is preferable to standard PLND for nodal staging. Notably, although ePLND is not associated with a significant risk of serious complications, up to 10% of the patients undergoing this procedure experience lymphoceles [57].

Statement 4: ‘PLND is not recommended in patients with low-risk PCa.’

The overall LNI rate is not significant in patients with low-risk PCa [56]. Several overseas guidelines [17,41,58] do not strongly recommend staging PLND in this group of patients. Considering the benefit–risk balance, PLND at the time of RP is not recommended in men with low-risk PCa.

Statement 5: ‘In patients with intermediate-risk PCa, ePLND should be performed when the estimated risk of lymph node metastasis is >5% based on nomograms.’

Statement 6: ‘Extended PLND should be performed in all patients with high-risk PCa.’

International guidelines [17,41,58] generally recommend PLND performed at the time of RP in patients with intermediate-risk PCa at significant risk of lymph node metastasis. The EAU recommendation, as described in the consensus statement, is applicable in the locality. For men

with high-risk PCa, the international guidelines share a common recommendation that all of these patients should undergo PLND at the time of RP. The panel generally agreed on the practice, and highlighted the use of ePLND, instead of standard PLND.

Despite the importance of PLND for nodal staging, a retrospective review of the pathology of >1000 PLNDs (extended or standard) [59] showed that, at a median follow-up of 4 years, only 10% of men with positive lymph node metastasis remained free of biochemical recurrence of disease, and only 5% had undetectable serum PSA. The number needed to treat with PLND to reach an undetectable post-RP PSA is ~400. In view of the low probability of being biochemically free of recurrent disease and the high number needed to treat for cure in men with lymph node metastasis, more research is warranted to identify the individuals who will benefit from PLND, possibly with the use of emerging radiological imaging tools.

Post-surgery care

Statement 1: 'The effectiveness of pelvic floor muscle training in improving urinary incontinence after surgery remains uncertain based on current literature; however, in view of its non-invasiveness, the behavioural exercise can still be considered to help with the recovery of continence function.'

As per two meta-analyses [60,61], neither pre- nor postoperative pelvic floor exercises offer a significant improvement in urinary incontinence. Nevertheless, the included studies had considerable variation in interventions, populations and outcome measures. More robust evidence from randomized controlled trials is required to further analyse the effect of pelvic floor exercises. Despite mixed evidence to date, pelvic floor exercises are still worth considering in patients who plan to undergo RP, because they are non-invasive and may potentially help improve continence function.

Statement 2: 'Penile rehabilitation with a daily low-dose phosphodiesterase 5 (PDE5) inhibitor should be offered to patients as soon as possible after surgery.'

In a trial that randomized patients who had undergone nerve-sparing RP to tadalafil 5 mg once daily, 20 mg on demand or placebo [62], at the end of the double-blind period (9 months), only those treated with tadalafil 5 mg once daily had a statistically significant improvement in erectile function compared with the placebo group. A sub-analysis of the study [62] also found that tadalafil 5 mg once daily was associated with a significantly reduced time to erectile function recovery during the 9-month treatment. Although its long-term efficacy needs to be further explored

[63], the early prescription of a daily low-dose PDE5 inhibitor is feasible to facilitate penile rehabilitation in patients who have undergone RP.

Radiotherapy

External beam radiotherapy

Statement 1: 'External beam RT (EBRT) should be a treatment option for patients with localized PCa, regardless of the risk category.'

Statement 2: 'Intensity-modulated RT (IMRT) is recommended as the standard of care for dose-escalated RT in all risk groups of localized PCa.'

External beam RT is a recognized principal treatment option for localized PCa, and multiple phase III randomized controlled trials [64–67] have shown that dose escalation (78 Gy vs 70 Gy) can improve biochemical control in patients with localized PCa from all risk groups. Compared with the conventional three-dimensional conformal RT (3D-CRT), IMRT, an advanced form of high-precision radiation that conforms the treatment volume to the prostate, is a safer approach to dose escalation and can spare more normal tissues, especially those in the rectum and bladder, in view of its dosimetry. A number of retrospective studies [68] have shown that IMRT results in similar biochemical control but fewer acute or late gastrointestinal (GI) or genitourinary (GU) complications compared to 3D-CRT among men with localized PCa. Despite no randomized trials directly comparing the two approaches, IMRT, instead of 3D-CRT, has become the standard dose-escalated RT for localized PCa [68–70].

In a retrospective study conducted in Hong Kong [71], a substantial proportion of patients with localized PCa achieved biochemical failure-free survival at 5 years after treatment with IMRT (95%, 82% and 80% for the low-, intermediate- and high-risk groups, respectively), with grade 2/3 late GI/GU toxicities observed in 3–8% of patients. These results are consistent with the outcomes of IMRT found in western countries, supporting the view that IMRT is effective and safe in local patients. On balance, IMRT is the standard dose-escalated RT for localized PCa, irrespective of the risk category.

Statement 3: 'Moderate hypofractionation (60 Gy/20 fractions in 4 weeks) can be considered as an alternative to conventional IMRT when clinically indicated.'

Radiobiological models suggest that PCa has a low $\alpha:\beta$ ratio of ~1.5 Gy, implying that the cancer cells are more sensitive to RT doses delivered in large fraction sizes rather than small ones [72]. A dose of 1.8–2 Gy/fraction is

regarded as conventional RT, whereas hypofractionated RT can be classified as moderate (2.4–4.0 Gy/fraction over 4–6 weeks) or extreme hypofractionation (i.e. stereotactic body radiotherapy [SBRT], 6–10 Gy/fraction, usually completed within five fractions of treatment). Despite no superiority found in the HYPRO trial [73], moderate hypofractionation (57–70 Gy in 2.5–3.4 Gy/fraction used in the trials) was similarly safe and effective compared to conventional fractionation in three large randomized non-inferiority trials [74–76]; therefore, moderate hypofractionation (60 Gy in 20 fractions over 4 weeks) can serve as an alternative to conventional IMRT in the treatment of localized PCa when clinically indicated.

Statement 4: ‘SBRT can be considered as an alternative to conventional IMRT at centres with appropriate facilities and clinical expertise.’

Over the past decade, phase I/II studies [77,78] have found that SBRT, or extreme hypofractionation, is comparable to conventional fractionation in terms of toxicity and efficacy. Hence, SBRT can be considered as an alternative to conventional IMRT in the treatment of PCa, if relevant facilities and experts are available. Notably, when SBRT is planned, image-guided RT (IGRT) is required to allow a safe and precise delivery of high-dose RT.

In Hong Kong, a phase II randomized trial comparing conventional IMRT with SBRT (7.5 Gy \times 5 fractions) has recently completed the patient accrual [79]. Apart from the clinical benefits, this ongoing trial will assess whether SBRT has a potential economic advantage and offers more convenience for patients because of its shorter treatment duration compared with conventional IMRT.

Statement 5: ‘IGRT, which includes the use of implanted fiducial markers, can be adopted with IMRT, moderately hypofractionated RT or SBRT to improve treatment accuracy.’

Intra- or inter-fractional prostate movements, either rotational, translational or deformational, may potentially jeopardize the accuracy of RT for PCa [80–85]. Obtaining imaging coordinates of the target tumour and healthy tissues before and during treatment, an IGRT system helps correct the random and systematic errors resulting from prostate movements, leading to a more accurate radiation delivery, and enhanced efficacy and safety of IMRT.

Despite there being no randomized dose-escalation trials on the use of IGRT systems, retrospective studies have shown that such technologies can improve biochemical and local control of PCa and reduce late GI/GU side effects. In the study conducted by the Memorial Sloan Kettering Cancer Center [86], a group of patients with PCa treated with IGRT based on kilovoltage imaging of implanted prostatic fiducial markers at a high dose of 86.4 Gy were retrospectively

compared with a similar cohort of patients treated with IMRT at the same dose but without implanted fiducial markers (non-IGRT). The results revealed that IGRT was associated with significantly less grade ≥ 2 late urinary toxicity compared with non-IGRT (3-year likelihood of the toxicity: 10.4% vs 20.0%; $P = 0.02$). The incidence of grade ≥ 2 rectal toxicity was low in both treatment groups (IGRT: 1.0% vs non-IGRT: 1.6%; $P = 0.81$). In comparison with non-IGRT, IGRT was associated with significantly improved PSA relapse-free survival in high-risk patients, although no such improvement was observed in low- and intermediate-risk patients. On balance, IGRT can deliver more accurate, more effective and safer RT for PCa compared with non-IGRT.

Clinical experience in Hong Kong has shown benefits of IGRT in patients with localized PCa. A local cohort study [87] showed that IGRT was associated with significantly less frequent, shorter-lived acute grade 1/2 GI toxicity compared with non-IGRT (23.8% vs 81.0%; $P = 0.001$; median duration: 0.33 weeks vs 1.38 weeks; $P = 0.004$). The frequency of acute grade 1/2 GU toxicity was similar in the two treatment groups (IGRT: 66.6% vs non-IGRT: 81.0%; $P = 0.45$). The IGRT group had a significantly shorter median PSA half-time than that of the non-IGRT group (3.36 weeks vs 5.49 weeks; $P = 0.09$). In short, IGRT is effective for reducing acute GI toxicity in the treatment of PCa and may have more favourable PSA kinetics compared with non-IGRT.

Commercially available IGRT systems include intraprostatic fiducial markers, cone-beam CT, the Calypso™ 4D system, and ultrasound localization. Of these, fiducial markers are the most widely used system in Hong Kong’s institutions. Despite the disadvantages of invasive implantation procedures using TRUS and the lack of intra-fractional monitoring, fiducial markers are relatively cost-effective compared with other systems [88]. They are worth using for IGRT, which can improve the accuracy, efficacy and safety of treatment when combined with IMRT or other RT approaches.

Statement 6: ‘Proton therapy is not recommended for routine clinical practice in the treatment of localized PCa.’

A proton beam has low incident energy and displays a spike at the tail-end of its dose distribution (i.e. the Bragg peak), with essentially no dose beyond the end range. In theory, proton therapy spares uninvolved tissues distal to a target tumour with a lower dose than photon beams [89]. Nonetheless, whether the theoretical dosimetric advantages of proton beams can translate into superior clinical efficacy compared with conventional photon RT remains uncertain. Some studies have investigated the use of proton beams in boosting conventionally fractionated EBRT for PCa [66,90–92]; however, to verify the efficacy and safety of proton therapy, randomized controlled trials are needed to directly compare its usage with that of photon RT. Indeed, there is an ongoing trial in the USA that is investigating proton therapy vs IMRT in

men with low- or intermediate-risk PCa [93], and the results are eagerly awaited. Aside from undetermined efficacy, another concern over proton therapy is the high cost of relevant facilities. Because of the uncertainty of its superiority over conventional photon RT, proton therapy is not currently recommended as routine treatment of localized PCa.

Role of pelvic radiotherapy

Statement 1: 'Pelvic RT should be considered only in patients with intermediate- or high-risk PCa.'

Statement 2: 'Pelvic RT should be performed by IMRT, instead of the traditional four-field RT technique.'

The role of pelvic RT in the treatment of PCa is unclear. In several trials that demonstrated the survival benefit of the combination of ADT and RT in men with high-risk PCa [94–96], almost all of the men had undergone pelvic RT, implying the importance of the procedure. In multiple surgical series [57], a significant portion of patients with high-risk PCa harboured nodal disease, as confirmed by ePLND, suggesting that it is reasonable to perform pelvic RT in men with high-risk PCa who plan to undergo RT. However, some physicians doubt the use of pelvic RT, as two randomized controlled trials demonstrated no significant benefits of the approach among patients with intermediate- or high-risk PCa [97–99]. In the randomized phase III Radiation Therapy Oncology Group (RTOG) 9413 trial, which used a 2×2 factorial design, although the initial result showed that, in combination with hormonal therapy, pelvic RT improved progression-free survival (PFS) compared with prostate-only RT [97], an updated analysis of the trial found no significant difference in PFS or OS between the two RT approaches among the patients alive after a median follow-up of 7 years [98]. Another trial, GETUG-01, found no significant difference in PSA-PFS between pelvic and prostate-only RT [99], but a main limitation of that study was that the upper border of the pelvic RT used was at the S1/S2 level, which is lower than the L5/S1 or L4/L5 in pelvic RT that is typically used for capturing at-risk pelvic nodes. To further investigate the role of pelvic RT, RTOG 0924, a phase III randomized trial [100], will recruit 2500 men with unfavourable intermediate- or high-risk PCa to receive ADT plus either prostate-alone or pelvic RT, with OS as the primary endpoint.

Because of this mixed evidence, most cancer centres in Hong Kong have not performed pelvic RT routinely in the treatment of PCa. At those centres that have experience in pelvic RT, the approach has been reserved only for patients with intermediate- or high-risk PCa, not low-risk disease. Meanwhile, pelvic RT should be performed with IMRT because of its dosimetric advantage over the traditional four-field RT technique. A Hong Kong study showed that, when used in pelvic RT, RapidArc™ IMRT had superior dosimetric outcomes and treatment delivery efficiency compared with conventional IMRT [101].

Brachytherapy Although the panel reviewed a number of articles on the efficacy and tolerability of brachytherapy [102–107], no consensus statements on this treatment option were reached. Indeed, the experience using brachytherapy in Hong Kong is limited, possibly because of the lack of expertise, high treatment and capital costs, and the wide acceptance of RP and EBRT among physicians and patients.

Post-radical prostatectomy radiotherapy

Statement 1: 'Post-RP patients with the following adverse pathological features could have a higher recurrence risk: (i) positive surgical margins; (ii) seminal vesicle invasion; (iii) extraprostatic spread; and (iv) Gleason score ≥ 8 .'

Of patients with localized PCa who have undergone RP, up to one-third may experience a PSA biochemical recurrence within 10 years [108]. If left untreated, a significant proportion of patients with recurrent disease may develop distant metastasis at 8 years after an increase in their PSA levels, followed by death from PCa at 5 years after the onset of metastatic disease [109]. In patients who have undergone RP, positive surgical margins, seminal vesicle invasion, extraprostatic spread, and a Gleason score of ≥ 8 are considered to be factors that could increase the risk of developing recurrent disease [109–113].

Statement 2: 'A biochemical recurrence after RP is defined as the detection of a PSA level at ≥ 0.2 ng/mL, with a second confirmatory level detected at ≥ 0.2 ng/mL, or the detection of one PSA reading of >0.4 ng/mL after RP.'

Statement 3: 'Adjuvant RT is the administration of RT to post-RP patients with adverse pathological features prior to evidence of disease recurrence (especially with an undetectable PSA level).'

Statement 4: 'Salvage RT is the administration of RT to the prostatic bed and possibly to the surrounding tissues, including lymph nodes, in post-RP patients with a detectable PSA recurrence but no evidence of distant metastatic disease.'

After discussion, the panel decided to adopt the definitions of post-RP biochemical recurrence, adjuvant and salvage RT from a guideline established jointly by the American Society for Radiation Oncology (ASTRO) and the AUA [114], which has been widely endorsed by local PCa experts. These definitions are expected to facilitate decision-making in the management of men with localized PCa who have undergone RP.

Statement 5: 'Adjuvant RT is an option for patients with adverse pathological features, with consideration of the patient's history, functional status, values and preferences, and his tolerance for the potential toxicities and impact on quality of life due to RT.'

In three randomized controlled trials and their follow-up analyses [115–120], adjuvant RT has been proven to improve biochemical control among patients with adverse pathological features following RP. One of the three trials, SWOG 8794, also showed that adjuvant RT was associated with significantly increased OS [116]. A retrospective cohort study demonstrated that adjuvant RT, compared with salvage RT, was associated with reduced biochemical recurrence, distant metastasis, and mortality for patients with adverse pathology [121]. Similar findings were presented in a Spanish nationwide cohort study, in which adjuvant RT yielded better 2- and 5-year biochemical relapse-free survival outcomes but equivalent OS rates compared with salvage RT [122].

One of the problems with adjuvant RT is the possibility of over-treatment. Local clinical experience has shown that about half of post-RP patients with adverse pathology do not develop recurrent disease in their lifetime. Given the possibility of over-treatment, adjuvant RT is not necessarily preferable to salvage RT. Another concern regarding adjuvant RT is that it should be performed within 3–4 months after surgery, during which time patients may not have fully recovered and may be RT-intolerant. Moreover, from a patient's perspective, if the post-RP PSA level remains low, the benefit of adjuvant RT may appear insignificant.

Although the evidence supports the use of adjuvant RT in post-RP patients with adverse pathology, a variety of considerations should be discussed thoroughly with the patient and his family before the treatment option is planned.

Statement 6: 'Salvage RT should be considered in patients with a persistently detectable post-RP PSA level.'

In the two randomized controlled trials, SWOG 8794 [115] and EORTC 22911 [117], some of the enrolled patients had a detectable PSA level at baseline (>0.2 ng/mL vs ≤ 0.2 ng/mL as undetectable) in the early post-RP period (<18 weeks). The subgroup analyses in each of the two trials showed that RT improved metastasis-free survival [116] and biochemical recurrence-free survival [118], with no significant difference attributable to the baseline post-RP PSA level (detectable vs undetectable). These results imply that, apart from adjuvant RT (initiated at an undetectable PSA level), salvage RT (at a detectable PSA level) can be considered as an alternative to treat post-RP patients with adverse pathology.

Statement 7: 'It is recommended to regularly monitor PSA levels in post-RP patients, in order to enable early administration of salvage RT whenever applicable.'

Statement 8: 'Early salvage RT should be considered when there is a detectable PSA level, i.e. ≥ 0.2 ng/mL.'

Salvage RT leads to better biochemical control when initiated at a lower PSA level, as shown in a systematic review [123].

Hence, physicians should regularly monitor the PSA levels in patients after RP, in order to initiate salvage RT as early as the PSA level becomes detectable, i.e. ≥ 0.2 ng/mL.

Statement 9: 'The minimum dose for salvage RT is recommended to be 64 Gy.'

To carry out salvage RT, IMRT, instead of 3D-CRT, should be considered, because it is associated with a lower risk of late GI toxicity [124,125]. In a retrospective analysis [126], there was a dose–response relationship between salvage RT (60–70 Gy) and relapse-free survival. According to an ASTRO/AUA guideline [114], 64 Gy is recommended as the minimum dose for salvage RT, ensuring effective disease control.

Statement 10: 'Regarding the clinical target volume for post-RP RT, the RTOG consensus guidelines should be followed.'

In the RTOG consensus [127], the prostate fossa clinical target volume for post-RP RT for PCa was defined and presented as a CT image atlas for physician reference. The definition is relevant and applicable to the local clinical setting.

Statement 11: 'The combination of salvage RT and hormone therapy in the treatment of localized PCa remains investigational.'

Data from randomized controlled trials investigating the use of salvage RT plus hormonal therapy in the treatment of localized PCa are few. In the RTOG 9601 randomized trial [128], the combination of 2-year bicalutamide, an antiandrogen, and salvage RT improved OS, disease-specific survival and metastasis-free survival compared with salvage RT alone in patients with recurrent disease after RP and a detectable PSA level of 0.2–4 ng/mL. From this, we may postulate that, for patients with a higher PSA level or pN1 disease at the time of salvage RT, the addition of hormonal therapy, including ADT, may be considered. RADICALS, an ongoing randomized trial in the UK [129], will investigate the outcomes of the combination of LHRH and salvage RT vs the combination of bicalutamide and salvage RT. At the present time, the combination of salvage RT and hormonal therapy in the treatment of localized PCa remains investigational.

Management of post-radiotherapy side effects

Statement 1: 'Treatment approaches to RT-induced proctitis include topical agents (e.g. steroid suppositories, formalin), oral medications, hyperbaric oxygenation (HBO), and endoscopic interventions (e.g. argon plasma coagulation [APC]).'

Proctitis is a common adverse event observed in patients treated with RT. Although the optimal management of RT-induced proctitis is ill-defined, there are a variety of possible treatment approaches, including topical agents, oral

medications, HBO and endoscopic interventions, such as APC. To treat newly developed proctitis, steroid suppositories can be initiated. If necessary, topical formalin can be applied with a cotton swab only to the area involved. HBO can be considered in patients with persistent severe proctitis. APC is reserved for patients with severe bleeding refractory to other measures, but its risk for further rectal injuries and clinical deterioration should be noted.

Statement 2: 'RT-induced proctitis is diagnosed endoscopically, without the need for histological confirmation, as biopsies may exacerbate the disease and are unlikely to provide useful information.'

In local clinical experience, proctitis in patients treated with RT can be diagnosed endoscopically, without the need for biopsies, which may only exacerbate the disease and are unlikely to offer useful information on diagnosis or treatment.

Statement 3: 'Before the treatment of cystitis, causes of haematuria other than RT, e.g. urinary calculi, tumours, infections, bleeding anomalies (medications and coagulopathies) and other non-bladder sources of bleeding (renal, ureter and prostate urethra), need to be ruled out by urine and serum tests, cystoscopy, and imaging.'

Apart from proctitis, haemorrhagic cystitis is another frequent problem experienced by patients after RT. To assess whether cystitis is induced by RT, urine and serum studies, cystoscopy and imaging should be performed to rule out other causes of haematuria, such as urinary calculi, tumours, infections, bleeding anomalies (due to medications or coagulopathies), and other non-bladder sources of bleeding (e.g. the kidneys, ureter or prostatic urethra).

Statement 4: 'Treatment modalities for haemorrhagic cystitis include continuous bladder irrigation, instillation of alum or formalin, fulguration with electrocautery, HBO, internal iliac embolization, intravesical hydrostatic pressure therapy, and cystectomy with urinary diversion (for extreme cases).'

While RT-induced cystitis is mostly self-limiting, a range of treatment methods can be considered when necessary. These include continuous bladder irrigation by three-way catheter with evacuation of clots, instillation of alum or formalin, fulguration with electrocautery, HBO therapy, internal iliac embolization, intravesical hydrostatic pressure therapy and, in extreme cases, cystectomy with urinary diversion.

Androgen Deprivation Therapy

Statement 1: 'ADT monotherapy should not be used in patients with localized PCa, regardless of the risk category.'

As a non-radical treatment approach, ADT monotherapy is not a standard of care for localized PCa. A large,

population-based study suggested that ADT monotherapy worsened OS of men with localized PCa compared with observation [130]. Randomized controlled trials [131,132] showed that ADT alone had significantly fewer OS benefits compared with the combination of RT and ADT among men with locally advanced PCa. Unless contraindications to radical treatment are present, ADT alone should not be considered in men with localized PCa.

Statement 2: 'ADT, with or without definitive local treatment, is not recommended in patients with low-risk PCa.'

As per the *post hoc* risk analysis of the RTOG 9408 trial [133], among patients with low-risk PCa, the addition of short-term ADT to RT did not significantly improve OS or disease-specific survival compared with RT alone. In view of this outcome, along with the evidence against the use of ADT monotherapy for localized PCa [130–132], ADT should not be used in men with low-risk PCa under any circumstances.

Statement 3: 'Neoadjuvant ADT for RP is not recommended.'

Although it can help to achieve pathological down-staging and improve positive surgical margin rates [134], neoadjuvant ADT before RP does not improve OS or disease-free survival among patients with localized PCa [135,136]. A Japanese study suggested that neoadjuvant ADT for low-risk PCa may increase the risk of biochemical recurrence after RP, because of upregulation of lymphangiogenesis-related variables [137]. In addition, there is a concern that pre-RP neoadjuvant ADT may complicate the procedure of surgery, especially nerve-sparing surgery, because of induced fibrosis. Consistent with international guidelines [17,58], the panel's consensus was that neoadjuvant ADT for RP is not recommended in patients with localized PCa.

Statement 4: 'Adjuvant ADT after RP is not recommended in patients with pN0 disease.'

Adjuvant ADT after RP is not recommended in patients with localized (pN0) PCa, because, despite the potential to improve PFS, it is unable to significantly increase OS in men with localized PCa [138]. Regarding adjuvant antiandrogen, a randomized trial found that its use improved neither PFS nor OS in men with localized PCa after RP [139].

Statement 5: 'When RT is planned for patients with intermediate-risk PCa, neoadjuvant ADT (for 4–6 months) can be considered.'

The combination of neoadjuvant ADT and RT can lead to significant survival benefits in men with intermediate-risk PCa compared with RT alone [133,140–143]; however, the optimal timing and duration of neoadjuvant ADT remain ill-defined. In the RTOG 9408 trial [133], the use of ADT for 4 months (starting 2 months before RT) was effective

to improve disease-specific survival and OS among patients with intermediate-risk PCa. The 4-month ADT schedule was further supported by the RTOG 9910 trial [141], which found that extending the ADT duration to 7 months before RT did not improve survival outcomes. Yet, a retrospective study conducted in Japan showed that neoadjuvant ADT lasting for ≥ 6 months improved biochemical recurrence-free survival in patients with intermediate-risk PCa [143]; therefore, neoadjuvant ADT for 4–6 months can be given before the initiation of RT for intermediate-risk PCa.

Statement 6: ‘When RT is planned for patients with high-risk PCa, neoadjuvant (for 4–6 months) and adjuvant ADT (for 2–3 years) are recommended.’

Similar to the efficacy in intermediate-risk PCa, ADT in combination with RT is able to significantly improve survival outcomes in men with high-risk PCa compared with RT alone [144]. Regarding the duration of ADT, the DART01/05 GICOR randomized controlled trial showed that, compared with only 4 months of neoadjuvant and concomitant ADT, additional adjuvant ADT continuing for 2 years after RT was associated with better biochemical control and OS among patients with high-risk PCa [96]. Based on a review [144], in addition to RT, ADT for ≥ 2 years can improve survival outcomes for locally advanced PCa. Based on the evidence, neoadjuvant (for 4–6 months) and adjuvant ADT (for 2–3 years) should be considered in patients with high-risk PCa who are expected to receive RT.

Statement 7: ‘To reduce the risk of ADT-related bone fracture, supplemental calcium and vitamin D should be considered in patients receiving ADT.’

Although short-term ADT added to RT causes no significant impact on health-related quality of life [145], long-term ADT may increase the risk of osteoporotic fracture in patients with PCa [146–148]. In these cases, calcium and vitamin D supplements should be considered as prophylaxis to prevent osteoporosis in patients treated with ADT.

Bone-protective agents, including bisphosphonates and denosumab, were also discussed by the panel members; however, it was stressed that patients should be alerted to the risk of osteonecrosis of the jaw associated with these medications [149]. Considering the benefit–risk balance, physicians seldom prescribe these agents for patients with localized PCa.

Statement 8: ‘The fasting lipid profile and cardiovascular risk of patients receiving ADT should be assessed regularly.’

Aside from bone fractures, cardiovascular side effects are another concern about the use of ADT in patients with PCa. Although the analyses of the RTOG 9408 and 9202 trials

found that ADT, irrespective of the duration, did not increase the risk of cardiovascular mortality in men with localized PCa [150,151], other studies have shown that ADT could increase weight gain and interfere with lipid profiles, potentially resulting in an elevated risk of cardiovascular events [152,153]. Some research suggested that the cardiovascular risk may depend on the type of ADT, but more detailed prospective evidence is required to verify the hypothesis [154]. In view of the clinical data, regular assessments of lipid profiles and cardiovascular risk should be considered as precautionary measures in patients treated with ADT.

Other Therapies

Statement 1: ‘Novel therapy and chemotherapy for localized PCa remain investigational and are not recommended for routine clinical practice.’

Researchers have started to study the use of novel agents, such as androgen receptor (AR) pathway inhibitors, in the treatment of localized PCa. Phase II studies have shown that the addition of neoadjuvant abiraterone to ADT prior to RT or RP can be effective for achieving prostatic androgen suppression, possibly reducing tumour burden in men with intermediate- or high-risk PCa [155,156]. Enzalutamide also may facilitate the treatment of PCa via the inhibition of the AR pathway. In a study in patients with intermediate- and high-risk PCa [157], neoadjuvant enzalutamide in combination with dutasteride and leuprolide before RP was effective for lowering concentrations of intraprostatic testosterone and PSA, suggesting a potential reduction in cancer burden.

Chemotherapy for the treatment of localized PCa is another emerging research topic. In a phase II trial of men with high-risk PCa [158], neoadjuvant paclitaxel, carboplatin and estramustine plus ADT before RP appeared to reduce the rates of biochemical recurrence and metastasis compared with RP alone, but the results were not statistically significant. Another phase II trial showed that, among men with locally advanced and high-risk PCa, neoadjuvant docetaxel plus complete androgen blockade prior to RP resulted in significant down-staging without pathological complete response and possibly improved the 5-year biochemical recurrence-free survival, but severe haematological toxicities were frequently observed [159]. Before more robust evidence is established, neoadjuvant chemo-hormonal therapy before RP should not be adopted in routine clinical practice, because of its high toxicity and unproven benefit.

Chemotherapy in addition to RT for the treatment of localized PCa has been attempted in some clinical trials. In the GETUG 12 randomized trial conducted in men with high-risk PCa [160], neoadjuvant docetaxel/estramustine plus ADT before local treatment (primarily RT) was associated

with a higher PSA response rate and had a favourable safety profile compared to ADT alone, but the impacts on relapse and survival need to be further assessed. Adjuvant chemotherapy after RT has also been studied. The RTOG 0521 phase III trial showed that, for high-risk localized PCa, adjuvant docetaxel and prednisone plus ADT after RT was associated with a higher 4-year OS rate (93% vs 89%; one-sided $P = 0.03$, HR 0.68, 95% CI 0.44–1.03) compared with ADT alone after RT, with an acceptable toxicity profile; however, the one-sided P value used in the statistical analysis is viewed as a limitation of the result, and additional research is warranted to investigate the long-term impact of adjuvant chemotherapy after RT [161]. With that benefit still under verification, the NCCN has recently suggested that docetaxel (without prednisone) may be administered after RT in selected patients with high-risk localized PCa who are fit for chemotherapy [41]. Nevertheless, in view of limited evidence, especially in the Chinese population, our panel have chosen to adopt a conservative stance and do not recommend the combination of chemotherapy and local treatment (RT or RP) for localized PCa.

Aside from AR pathway inhibitors and chemotherapy, other novel agents, such as those targeting different growth factor receptors and immunotherapies, are under investigation for the treatment of localized PCa [162]. To date, novel therapies and chemotherapy for localized PCa remain investigational and should not be used in routine clinical practice.

Part 6: Follow-up and Monitoring after Definitive Local Treatment

Recurrence After Surgery

Statement 1: ‘A reasonable schedule for PSA monitoring after RP is to test the PSA level: (i) every 3 months in year 1; (ii) every 6 months in year 2; and (iii) annually thereafter.’

After reviewing several international guidelines [41,58,163] and considering their practicability and suitability in the locality, the panel decided to adopt the PSA testing schedule proposed by a group of PCa experts in Canada for men who have undergone RP for localized PCa [163].

Statement 2: ‘It is recommended to check the PSA level of post-RP patients annually until the end of their life, but physicians should determine at their discretion whether to stop testing in patients who are unlikely to benefit from salvage therapy, e.g. those with a life expectancy of <5 years.’

Although an annual PSA check is recommended in post-RP patients, some circumstances may allow the termination of follow-ups. According to a long-term review conducted in Japan [164], if a patient’s PSA level is undetectable by ultrasensitive assay for 5 consecutive years, the PSA

monitoring may be halted because the risk of subsequent biochemical recurrence will be extremely low. Another situation in which PSA testing may be stopped is when the patient may no longer benefit from salvage therapy in view of life expectancy [163].

Recurrence After Radiotherapy

Statement 1: ‘A biochemical failure after RT, with or without hormone therapy, is defined as a rise in the PSA level by ≥ 2 ng/mL above the PSA nadir.’

Based on clinical experience, men who have received RT for localized PCa often take 6–18 months to reach a PSA nadir compared with 6 weeks to 2 months for patients who have undergone RP. To define biochemical failure after RT, the Phoenix definition has been the international standard for the past decade [165].

Statement 2: ‘The definition of secondary biochemical progression after postoperative salvage RT remains undetermined but is usually considered as a rise in the PSA level by ≥ 0.2 ng/mL above the post-RT nadir.’

Despite a lack of high-level agreement in the literature, the definition of secondary biochemical progression after postoperative salvage RT can be considered as a rise in the PSA level by ≥ 0.2 ng/mL above the post-RT nadir, as per a large retrospective analysis series conducted in the USA [166].

Statement 3: ‘A reasonable schedule for PSA monitoring after RT is to test the PSA level: (i) 6 months after treatment completion; (ii) every 6 months until the end of year 5; and (iii) annually thereafter.’

Similar to that for men who have undergone RP (Section Recurrence After Surgery, Statement 1), the schedule for PSA testing in patients who have received RT was adopted from the Canadian expert group [163].

Diagnostic Imaging After Biochemical Relapse

Statement 1: ‘When salvage RT is planned after RP in patients with a PSA level <1 ng/mL or a PSA doubling time (PSADT) ≥ 6 months, no diagnostic imaging is recommended.’

Referring to the section Post-RP RT, Statement 8, when there is a detectable post-RP PSA level, i.e. ≥ 0.2 ng/mL, early salvage RT should be considered. To treat biochemical recurrence after RP in patients with a PSA level <1 ng/mL or a PSADT ≥ 6 months, salvage RT is often planned; however, no diagnostic imaging is recommended because the possibility of detecting lymph node or distant metastases is low, either by a bone scan, CT scan or PSMA PET [24,167,168].

Consequently, the imaging results are unlikely to affect the treatment decision.

Statement 2: 'In the setting of post-RP biochemical recurrence, in cases of a PSA level ≥ 1 ng/mL or a PSADT < 6 months, whole-body PSMA PET-CT can be considered to detect the presence of pelvic lymph node or distant metastases, in order to guide the treatment decision.'

According to a systematic review and meta-analysis of 16 articles involving 1309 patients [24], positive rates of biochemical recurrence on ^{68}Ga -PSMA PET after RP increased with pre-PET PSA levels. For the PSA ranges 0–0.2, 0.2–1, 1–2 and > 2 ng/mL, 42%, 58%, 76% and 95% of the scans, respectively, were positive on metastases. In addition, the review found that a shorter PSADT was associated with increased ^{68}Ga -PSMA PET positivity (PSADT ≥ 6 vs < 6 months, positivity = 64% vs 92%) [24]. Based on these results, for post-RP biochemical recurrence, if a PSA level is ≥ 1 ng/mL or PSADT is < 6 months, whole-body PSMA PET-CT can be considered to detect the presence of pelvic lymph node or distant metastases, in order to assess whether to use salvage RT or other treatment measures; however, it was noted that further prospective trials are eagerly awaited to confirm the clinical benefits of this imaging method.

Statement 3: 'In the setting of post-RP biochemical recurrence, in cases of a PSA level ≤ 10 ng/mL, whole-body PSMA PET-CT may be more sensitive than a bone scan or CT scan in the detection of pelvic lymph node or distant metastases.'

Based on retrospective analyses [167,168], patients with biochemical recurrence after RP have a low probability of positive bone scan or positive CT scan, unless they have a high PSA level (> 10 ng/mL). As discussed in Statement 2, ^{68}Ga -PSMA PET is worth considering in patients with post-RP biochemical recurrence who have a PSA level ≥ 1 ng/mL; therefore, in the setting of biochemical recurrence after RP, in cases of a PSA level ≤ 10 ng/mL, whole-body PSMA PET-CT may be more sensitive than a bone scan or CT scan in the detection of pelvic lymph node or distant metastases.

Statement 4: 'In the setting of post-RT biochemical recurrence, in cases of a PSA level > 10 ng/mL, further imaging using bone scan, CT scan or whole-body PSMA PET-CT scan can be considered to guide the treatment decision.'

Based on the evidence discussed for Statements 2 and 3 [24,167,168], regarding biochemical recurrence after RT or RP, in cases of a PSA level > 10 ng/mL, either a bone scan, CT scan or whole-body PSMA PET-CT is sensitive enough for the detection of lymph node or distant metastases, and will help to guide the treatment decision.

Part 7: Management of De Novo Pelvic Nodal Disease (with Evidence of Pelvic Lymph Node Metastasis on Presentation, but M0)

Statement 1: 'In patients diagnosed with N1M0 disease on presentation, ADT alone \pm EBRT to the primary tumour can be considered.'

In a *post hoc* analysis of the STAMPEDE trial [169], among patients with N+M0 disease, RT (prostate \pm whole pelvis) plus ADT was associated with better failure-free survival compared with ADT alone (HR 0.48, 95% CI 0.29–0.79; 2-year failure-free survival: 81% vs 53%). Similarly, a large retrospective study conducted in the USA [170] showed that, compared with ADT alone, ADT plus RT was associated with a lower risk of 5-year all-cause mortality (HR 0.50, 95% CI 0.37–0.67, two-sided $P < 0.001$; crude OS rate: 71.5% vs 53.2%) in men with cN+ M0 PCa. These results suggest that long-term ADT \pm RT can be considered in patients with N+

Fig. 1 Diagnostic evaluation and staging for suspicious localized prostate cancer (PCa). *Free/total (f/t) PSA ratio or prostate health index (PHI) may aid counselling for the decision on whether to perform a prostate biopsy. [†]TRUS-guided biopsy with 10–12 cores is recommended. [‡]Multiparametric (mp)MRI or combination of systematic and MRI-targeted biopsies (either with cognitive guidance or mpMRI/ultrasonography fusion) can be offered. ISUP, International Society of Urological Pathology; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

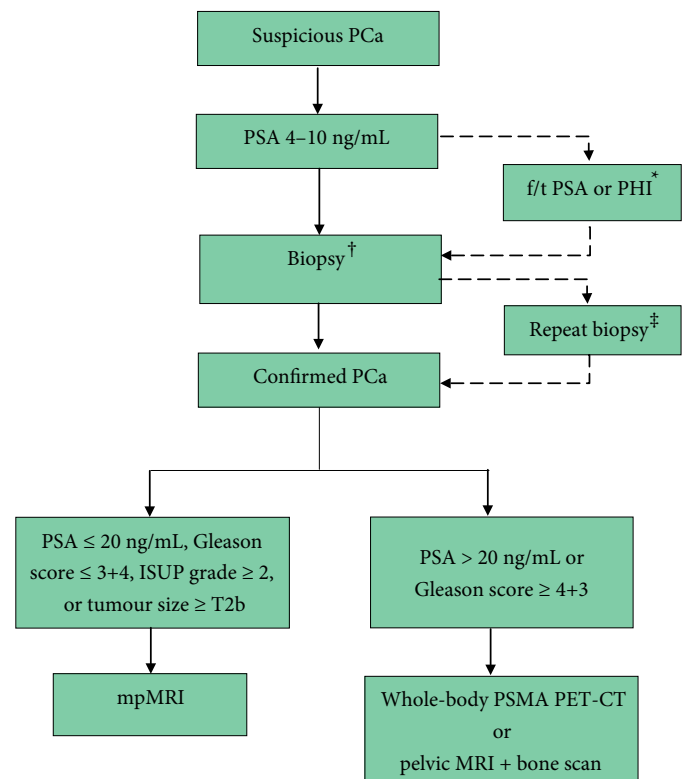
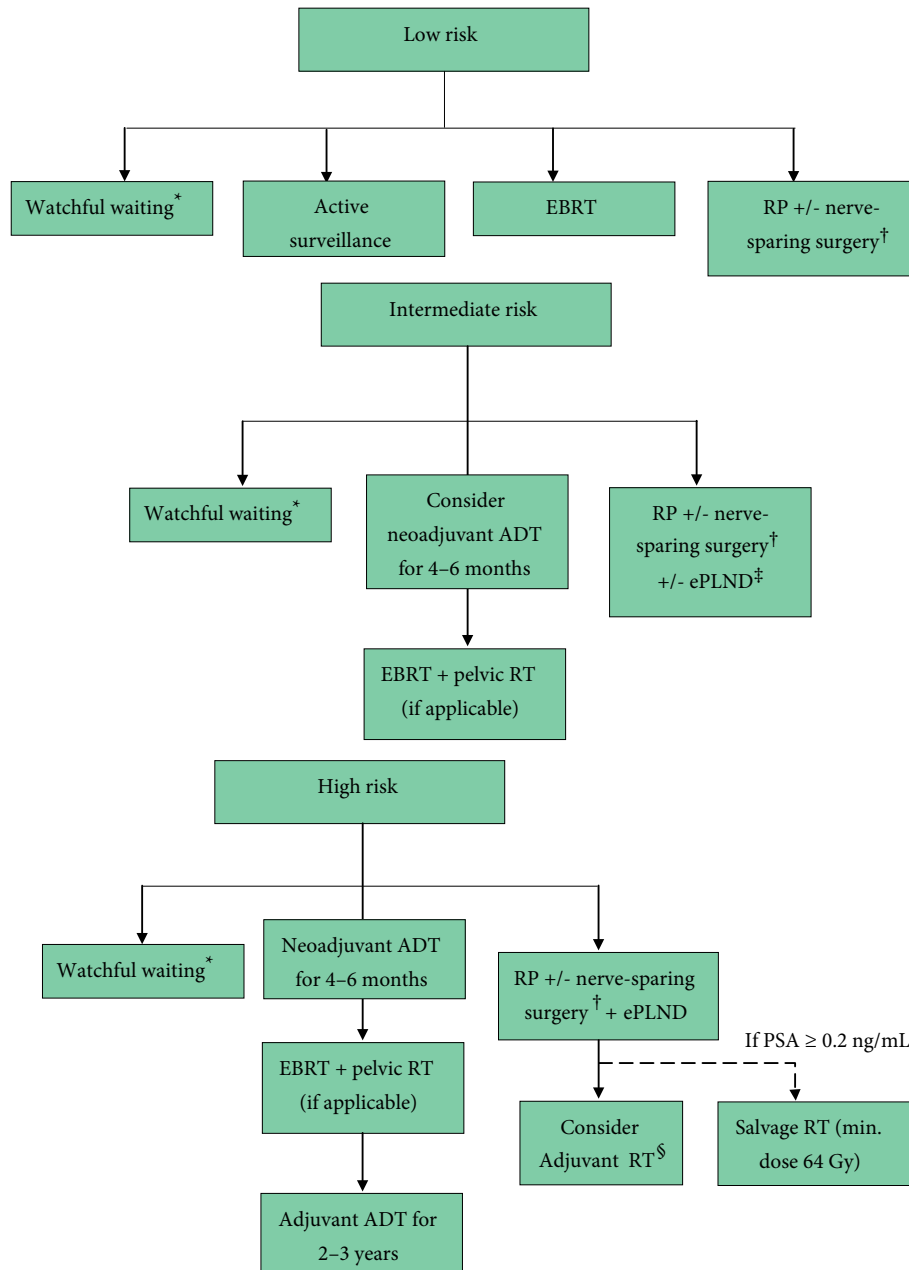


Fig. 2 Localized prostate cancer treatment algorithm. *Offer to patients not eligible for local curative treatment (e.g. poor pre-morbid status) and those with a short life expectancy (<10 years). †Offer to patients with a low risk of extracapsular disease (based on nomograms). ‡Offer when the estimated risk of lymph node metastasis is >5% based on nomograms. §With consideration of the patient's history, functional status, values and preferences, and his tolerance for the potential toxicities and impact of radiotherapy (RT) on quality of life. ADT, androgen deprivation therapy; EBRT, external beam radiation therapy; ePLND, extended pelvic lymph node dissection; RP, radical prostatectomy.



M0 disease. In the panel's experience, surgery is seldom performed for N+ M0 disease.

Statement 2: 'Survival benefits of immediate ADT after RP in patients with pathological pelvic lymph node metastasis remain uncertain.'

Although one study, conducted in an era when serum PSA testing was not widely used for the diagnosis of PCa, showed

that immediate antiandrogen therapy after surgery improved survival and reduced the risk of recurrence in patients with N+ PCa [171], the more recent Surveillance Epidemiology and End Results (SEER)-Medicare cohort study [172] revealed that deferring immediate ADT in men with N+ PCa after RP did not significantly compromise survival. In the EORTC 30846 randomized trial [173], among patients with pN1-3 M0 PCa without local treatment of the primary tumour, no

significant difference in OS or PCa-specific survival was observed between immediate and delayed ADT, although the trial was underpowered to confirm non-inferiority. In view of the evidence, survival benefits of immediate ADT after RP in men with pN+ PCa remain uncertain.

Statement 3: 'Men with low-volume nodal disease (two pelvic lymph nodes) in the presence of intermediate- or high-grade, non-specimen-confined disease, and those with intermediate-volume nodal disease (three or four pelvic lymph nodes) represent the ideal candidates for adjuvant RT after surgery.'

In a retrospective cohort study of men with pN1 PCa treated with RP and ePLND [174], the multivariable analysis showed that adjuvant RT plus ADT was associated with reduced cancer-specific mortality compared with adjuvant ADT alone (HR 0.37; $P < 0.001$). However, the sub-group analysis found that only two risk groups of men benefited from adjuvant RT plus ADT: (i) patients with a positive lymph node count of 2, Gleason score 7–10, pT3b/pT4 stage, or positive surgical margins (HR 0.30; $P < 0.002$); and (ii) patients with a positive lymph node count of 3–4 (HR 0.21; $P < 0.02$), irrespective of other tumour characteristics. These results imply that men with low-volume nodal disease (two positive lymph nodes) in the presence of intermediate- to high-grade, non-specimen-confined disease and those with intermediate-volume nodal disease (three to four positive lymph nodes) represent the ideal candidates for adjuvant RT after surgery.

Statement 4: 'In patients with pelvic lymph node recurrence after surgery, the combination of ADT and salvage pelvic RT can be considered.'

Based on the above evidence regarding the treatment of N+ M0 disease, the combination of ADT and salvage pelvic RT can be considered for the treatment of pelvic lymph node recurrence after surgery, although more research should be done. In the panellists' experience, surgery is seldom performed for post-RP pelvic lymph node recurrence.

Discussion

Based on current published evidence and the panellists' clinical experience, consensus statements on the management of clinically localized PCa for Hong Kong have been established for dissemination. Adapted from the consensus statements, two figures demonstrate the key processes of the diagnostic evaluation for suspicious PCa (Fig. 1) and the treatment algorithm (Fig. 2). Notably, there are still some questions remaining in the management of localized PCa, in particular those related to the clinical benefits of new-generation imaging tools, the survival benefits of salvage RT plus ADT, the use of novel therapy, and the benefits of immediate ADT after RP in men with pN+ PCa. Prospective trials, especially those conducted in Chinese or Asian patients,

are eagerly awaited to address these queries. In the face of emerging data from ongoing clinical research, consensus statements are subject to regular review and necessary updating. In conclusion, these statements are aimed to serve as recommendations for physicians in Hong Kong for the management of localized PCa.

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Conflict of Interest

None declared. Conflict of interest statements from all panellists are listed in Appendix S3.

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Abbreviations: PCa, prostate cancer; HKUA, Hong Kong Urological Association; HKSUO, Hong Kong Society of Uro-Oncology; RP, radical prostatectomy; f/t PSA, free/total PSA; PHI, prostate health index; NICE, National Institute for Health and Care Excellence; PSMA, prostate-specific membrane antigen; PET, positron emission tomography; ISUP, International Society of Urological Pathology; RT, radiotherapy; HR, hazard ratio; ADT, androgen deprivation therapy; EAU, European Association of Urology; NCCN, National Comprehensive Cancer Network; OS, overall survival; LRP, laparoscopic radical prostatectomy; RARP, robot-assisted radical prostatectomy; ORP, open radical prostatectomy; PLND, pelvic lymph node dissection; ePLND, extended pelvic lymph node dissection; LNI, lymph node invasion; PDE5, phosphodiesterase 5; EBRT, external beam radiotherapy; IMRT, intensity-modulated radiotherapy; 3D-CRT, three-dimensional conformal radiotherapy; GI, gastrointestinal; GU, genitourinary; SBRT, stereotactic body radiotherapy; IGRT, image-guided radiotherapy; RTOG, Radiation Therapy Oncology Group; PFS, progression-free survival; ASTRO, American Society for Radiation Oncology; HBO, hyperbaric oxygenation; APC, argon plasma coagulation; AR, androgen receptor; PSADT, PSA doubling time.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. The modified Delphi method aimed at reaching consensus.

Appendix S2. Full voting records for each drafted statement.

Appendix S3. Summary conflict of interest statements from all panellists.