These guidelines have been withdrawn

MOH clinical practice guidelines are considered withdrawn five years after publication unless otherwise specified in individual guidelines. Users should keep in mind that evidence-based guidelines are only as current as the evidence that supports them and new evidence can supersede recommendations made in the guidelines.

CLINICAL PRACTICE GUIDELINES

Prostate Cancer

Ministry of Health

NMRC National Medical Research Council

National Committee On Cancer Care

May 2000

MOH Clinical Practice Guidelines 3/2000

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Statement of Intent

These guidelines are not intended to serve as standards of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

Foreword

Cancer has been a leading cause of death in Singapore since 1991. In 1999, it accounted for nearly 27% of all deaths. The key components in cancer control include prevention, early detection and effective treatment. The Ministry of Health appointed the National Committee on Cancer Care (NCCC) in January 1998 to advise on the formulation of policies on cancer care and to plan for cancer services in Singapore. One of the approaches adopted to improve cancer care using an evidence-based approach is to produce a series of clinical practice guidelines on the cancers commonly occurring in Singapore, one of which is prostate cancer.

As the incidence of prostate cancer increases with age, many men are at risk of this disease in our ageing population. The difference in the incidence and screening pick-up rate amongst Asian and Western populations prompts us to re-interpret some of the data published by the Western countries. The physical and psychosocial morbidities, together with the various therapies available, make the management of prostate cancer challenging.

These guidelines present a comprehensive documentation on the management of prostate cancer for all clinicians. It also gives the direction on future research of prostate cancer in Singapore.

DR CHEN AI JU
DIRECTOR OF MEDICAL SERVICES

Contents

1 Introduction

1.1 Prostate cancer in Singapore

Prostate cancer is the sixth commonest cancer among men in Singapore.* While the incidence is substantially lower than that in many Western countries, it has been increasing even after having corrected for life expectancy. Furthermore, the majority of patients with prostate cancer present with locally advanced and/or metastatic disease at the time of first diagnosis. The prognosis of advanced prostate cancer is poor despite the most aggressive treatment. Cure is impossible for metastatic prostate cancer. The median time to progression and median survival is approximately 18 and 30 months respectively. Such data contrast sharply with the results of treatment for localised disease where median survival has been shown to be longer than 15 years. The observed crude survival rates are identical to the expected survival of age-matched controls. As such, it is reasonable to strive for early diagnosis and treatment in the hope of survival benefits. However, uncertainties of the natural history of the disease and efficacy of treatment due to the lack of randomised control studies still cast doubts on the potential benefits of a screening programme.

1.2 Guideline development and target group

Workgroups comprising members from the Singapore Urological Association and the Asian Society for Uro-oncology were formally appointed by the National Committee on Cancer Care to formulate clinical practice guidelines on urogenital cancers. The workgroup developing guidelines on the management of prostate cancer presented the draft to a panel of international and regional experts. All the relevant issues were discussed thoroughly till a consensus was achieved.

* Singapore Cancer Registry. Trends in cancer incidence in Singapore, 1968-1992.

These guidelines are prepared for clinicians who are involved in the care of patients with prostate cancer. The guidelines cover a wide range of issues; some of them may not be immediately relevant to subspecialty practitioners while others remain as issues for future research due to the paucity of evidence in the literature. Revisions would be necessary when new evidence becomes available.

More information on the topic is available on the following websites:

http://www.cancernetwork.com/indexes/nccn.htm
http://cancernet.nci.nih.gov/clinpdq/soa.html
http://www.urology-singapore.org/html/index.html

2 Levels of evidence and grades of recommendation

Levels of evidence

Level	Type of Evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Grades of recommendation

Grade	Recommendation
A (evidence levels Ia, Ib)	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
B (evidence levels IIa, IIb, III)	Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.
C (evidence level IV)	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality.
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group.

3 Executive summary of recommendations

Screening and diagnosis

A Population screening for prostate cancer among Asians is not recommended.

Grade A, Level Ia

B The appropriate threshold prostate specific antigen (PSA) level for case detection is 4.0 ng/ml.

Grade B, Level IIb

B The combination of digital rectal examination (DRE) and PSA enhances early detection.

Grade B, Level IIa

A Prostate biopsy is recommended for patients with abnormal PSA results and/or suspicious DRE.

Grade A, Level Ib

B Imaging modalities, including transrectal ultrasound (TRUS), computed tomography (CT) and magnetic resonance imaging (MRI), have limited value in diagnosis and staging.

Grade B, Level III

B There may be a role for CT/MRI in the staging of patients with high risk of nodal metastasis.

Grade B, Level III

Treatment

The choice of treatment between surveillance, surgery and radiation for localised prostate cancer should be individualized and based on an assessment of the biological potential of the disease, the life expectancy of the patient and the preference of the patient. There is no clear-cut evidence available showing definite advantage of one over the others.

B The potential benefits of surveillance in patients with low grade, low volume tumour and elderly patients with limited life expectancy are the absence of complications compared to conventional radiotherapy or radical surgery and the minimal costs involved.

Grade B, Level III

B The patient who is most likely to benefit from surgery would have a clinically organ-confined disease, a relatively long life expectancy, no significant surgical risk factors and a preference to undergo surgery. Radical prostatectomy should be considered in particular for the high risk group (i.e. Gleason's sum >6, stage T2c or PSA<20 ng/ml).

Grade B, Level III

B The long term results of radiotherapy in stage T1 and T2 patients are similar to those reported with radical prostatectomy despite differences in case selection and the lack of surgical staging of the lymph nodes in most cases.

Grade B, Level III

A Hormonal therapy remains the mainstay of treatment for metastatic prostate cancer. Surgical castration is equal in efficacy compared with other means of medical castration, including total androgen blockage.

Grade A, Level Ib

A None of the second line treatment options has shown consistent advantage. The choice of treatment should again be individualized.

Grade A, Level Ib

4 Screening & diagnosis of prostate cancer

4.1 Screening

Although some guidelines advocate annual digital rectal examination (DRE) and prostate specific antigen (PSA) test for men above 50 years of age, there is currently insufficient scientific evidence to show a decrease in mortality from prostate cancer by screening.[1-4]

At present, screening is not recommended among Asians.**(A/Ia)** However, all males above 40 years of age with the risk factor of having a first degree relative with prostate cancer at young age (<60 years) may be screened.**(GPP)**

4.2 Diagnosis

Patients usually only develop symptoms in the advanced stages of the disease. The majority of cases of early prostate cancer are diagnosed incidentally at transurethral resection of the prostate for benign prostatic hypertrophy (BPH) or by individualized testing.

4.3 Tests for screening and diagnosis of prostate cancer

4.3.1 Prostate specific antigen (PSA)

PSA is the most useful test in the detection of prostate cancer in Western countries. The value of PSA in Asians is less clear, compared with DRE and TRUS, partly because of the lower incidence of prostate cancer in the population.[5,6] The appropriate threshold PSA level for the detection of cancer of the prostate is 4.0 ng/ml.[7-10] **(B/IIb)** Clinically significant cancers are detected by PSA testing.[4,8,11]**(B/IIa)** PSA-based screening has induced a stage migration,[4,13] but only very preliminary indications of improved survival are available.[7]**(C/IV)**

Age-specific PSA ranges were devised to improve the detection of clinically significant cancer for the younger patients and improve

specificity in the older ones. However, the improved sensitivity and specificity is at best modest and hence not recommended.[12,14]

PSA velocity (0.75 ng/ml/yr) has not improved the sensitivity and specificity of the test and is probably not useful as first line assessment for cancer of prostate.[15,16]

PSA density is not recommended as there is no improvement in the sensitivity and specificity over the PSA level.[17-20]

The ratio of free to total PSA levels is recommended as the sensitivity and specificity of PSA levels at 2 –10 ng/ml for detecting cancer of the prostate is higher.**(B/IIa)** However, the optimal cut-off level is still being investigated.[21-23]

4.3.2 Digital rectal examination (DRE)

DRE is recommended as the combination of DRE and PSA test enhances early prostate cancer detection.**(B/IIa)**

4.3.3 Transrectal ultrasound guided biopsy

Prostate biopsy is recommended for patients with abnormal PSA results and/or suspicious DRE.[4,6]**(A/Ib)**

The standard sextant technique of needle biopsy uses a transrectal approach under ultrasound guidance. More number of cores may be needed if hypoechoeic and/or suspicious lesions are present, especially in large prostates.[24] Transrectal ultrasound alone has little value in the definitive diagnosis of prostate cancer.

Transrectal ultrasound guided needle biopsy is a safe procedure with few major but frequent minor complications. The use of antibiotics for aerobic and anaerobic bacterial coverage is to be considered; little consensus is available on the most appropriate regimen.[25,26]**(B/III)**

Prostatic biopsy should be repeated in patients with normal histology but suspicious DRE or persistently elevated/rising serum PSA.[27,28] Biopsy at additional sites, including lesion directed biopsies, lateral

peripheral zone biopsies and mid zone biopsies, etc. may also increase the diagnostic yield.[28,29]

Biopsy findings of high grade prostatic intraepithelial neoplasia (PIN grades 2 and 3) and invasive prostate cancer necessitate further investigations in patients who are candidates for radical treatment of localised prostate cancer.[30,31]**(B/IIb)**

5 Staging of prostate cancer

5.1 Investigations for staging of prostate cancer

Decisions regarding treatment options are dependent on the assessment of the biological potential of the disease, the overall health of the patient and the available treatment expertise. The current staging and grading methods of prostate cancer strive to provide a reliable predictor of the aggressiveness of the disease (Annex 1). However, clinical staging using DRE and imaging methods suffers from lack of specificity. A significant number of patients with clinically localised disease have locally advanced disease at surgery. Though the Partin tables* apply consistently to populations of Asians in predicting organ-confined disease, there is significant under- and overstaging based on clinical parameters. As such, more tests have evolved to stage the disease accurately before treatment plans.

- **DRE** – This is not recommended as a precise staging modality as the finding may differ significantly from the actual pathological stage. Concurrent prostatic diseases like BPH, prostatitis, previous prostatic biopsy or surgery could make the assessment more difficult. [32,33]**(B/ III)**

- **Prostatic Acid Phosphatase (PAP) and Alkaline Phosphatase (ALP)** – These are less useful compared with PSA.

- **PSA –** A serum PSA level of < 10 ng/ml indicates a lower risk of peri-prostatic spread and metastasis. An increased risk of extra-capsular extension or seminal vesicle involvement and even distant metastasis may be indicated with PSA levels of $\geq$10 ng/ml. As a general guide, if PSA is >10 ng/ml, more than 50% have capsular penetration; if PSA is > 50 ng/ml, the majority have pelvic lymph node involvement. [34]**(B/ IIb)**

* Partin, in 1997, devised a system (including preoperative PSA, clinical staging and Gleason grading) to predict the final pathological stage at surgery.

- **Transrectal ultrasound –** Transrectal ultrasound alone is of limited value for the staging of prostate cancer.[36,37] The increasing number of positive biopsy cores and the presence of perineural invasion have negative prognostic implications.[34]**(B/III)**

- **Pelvic lymph node dissection** – This remains the most accurate method of assessing nodal metastasis. However, patients with low risk disease (PSA < 10 ng/ml, Gleason's sum < 7 and stage T1c disease) have < 5% chance of having lymph node involvement. As such, only high risk patients with stage T3c or node positive disease should be recommended for pelvic lymph node dissection before definitive treatment for localised prostate cancer.[34,38] **(B/IIb)**

- **Seminal vesicle biopsy –** This is not recommended as it does not add significantly to the combination of clinical staging, PSA and Gleason score, which predicts seminal vesicle involvement to an acceptable degree.[34]**(B/IIb)**

- **Computed tomography (CT) and magnetic resonance imaging (MRI)** - The current role of CT and MRI in the staging of localised prostate cancer is rather limited. Most of the microscopic features of extra-capsular spread, seminal vesicle invasion and pelvic node metastasis are not obvious in radiological films. Inter-observer variation has also been reported. However, there may be a role for CT/MRI in the staging of patients with high risk of nodal metastasis.[36,39,40-42]**(B/III)** MRI may also be useful in cases of high clinical suspicion of bone metastases with inconclusive bone scan or probable vertebral pathology leading to a spinal cord problem.[43,44]

- **Bone scan** – This is the most sensitive method for detecting bone metastasis. However, in cases with PSA < 10 ng/ml, the probability of a positive scan is low in the absence of bone pain. Bone scans can be omitted in these patients.**(B/III)**

6 Treatment of localised prostate cancer

No recommendation can be made on the relative merits of the various treatment strategies in terms of overall mortality and cancer-related mortality because of insufficient evidence. Patients diagnosed to have prostate cancer should be counselled on the available options including surveillance alone, surgery, radiation or a combination of these.

The various treatment modalities and the follow-up plans are discussed in the following sections.

6.1 Surveillance

Current evidence suggests that patients with low volume, low grade prostatic carcinoma may be asymptomatic for prolonged periods. Eighty percent of the autopsies of men who died of other causes showed occult prostatic carcinoma. The overall survival of patients with clinically localised prostatic carcinoma was not statistically different from the life-table probability for men of similar age-group.[45,46] Of those under expectant management for more than 10 years of follow-up, the cause of death was not prostatic carcinoma.[47,48] Surveillance alone has been shown to achieve comparable results with other treatment modalities, namely conventional external beam radiotherapy and radical surgery. Most series achieve 80-90% 10-year survival rates after excluding deaths from intercurrent diseases.

The potential benefits of surveillance in patients with low grade, low volume tumour and elderly patients with limited life expectancy are the absence of complications compared to conventional radiotherapy or radical surgery and the minimal costs involved.**(B/III)**

Follow-up assessment includes 6-monthly consultation with routine DRE and serum PSA (refer to section 5). Prostatic biopsy and bone scans may be indicated.[48]

PSA surveillance is recommended as post-primary treatment follow-up of localised disease. A doubling of PSA levels in less than 6 months post-treatment may suggest systemic progression.[35]

6.2 Radical Prostatectomy

With the widespread use of PSA, more patients are found with organ-confined disease, and curative measures by surgical removal of the cancer can be achieved.[4,49] Surgery also offers more accurate staging, allowing better planning for adjuvant therapy.

An assessment of the biological potential of the disease, the life expectancy of the patient, the preferences of the patient and availability of expertise are important considerations in establishing the choice of therapy for localised prostate cancer.[50] The results of non-randomized retrospective reviews showed that 10 and 15 years actuarial survivals are 10-15% better after surgery than radiation or surveillance, particularly for the high-risk group, i.e. Gleason's sum > 6, stage T2c or PSA < 20 ng/ml.[49,51-55]**(B/III)**

Patients with clinically organ-confined disease, relatively long life expectancy and no significant surgical risk factors are most likely to benefit from surgery.[56] Young patients in the high-risk group may benefit from surgery.**(B/IIa)**

In selected individuals with prolonged life expectancy, surgery may be offered for clinical stage T3 disease.**(B/III)** For patients with stage T1a and T1b disease, surgery is an option for patients < 70 years of age with intermediate or high-risk disease, e.g. T1b with Gleason's sum > 5. The additional morbidity associated with radical prostatectomy after TURP should be considered.[58]**(B/III)**

Gross locally advanced disease (e.g. presence of hydronephrosis), failure after radiation and patients with less than 10 years life expectancy are contra-indications to radical prostatectomy.[59,60] **(B/ III)**

As radical prostatectomy carries significant morbidity, a thorough evaluation of the patient's co-morbidity and discussion of options are recommended.**(B/III)**

Short-term morbidity includes intraoperative bleeding, rectal injury, pulmonary embolism, myocardial infarction and infective complications. Long-term morbidity includes incontinence, impotence and bladder neck contracture.[56,64,65] Erectile dysfunction is common even after nerve sparing procedures.[66] Overall morbidity may be higher than that reported from large institutions.[67]

Intraoperative pelvic lymph node dissection may be omitted in patients with low PSA, low Gleason's score and clinically early disease.[61,62,34]**(B/III)**

Both perineal and retropubic prostatectomy give comparable results in terms of morbidity and disease-free survival.[63]**(B/III)**

Neoadjuvant hormone therapy has not resulted in improved survival and is not recommended currently.[68,69]**(B/IIb)** Planned adjuvant hormonal therapy or radiotherapy for locally advanced disease prolongs disease-free interval but the impact on survival is not clear. The option of adjuvant/salvage therapy should be considered after failed definitive therapy.[70] Some series have reported good long term results for patients with locally advanced disease after surgery and adjuvant hormonal therapy.[57]

PSA levels should be taken at 4-6 weeks post-operation, followed by 6-monthly PSA levels for 10 years, and yearly PSA levels thereafter. DRE should be performed at every visit. Bone scans, CT scans and prostate bed biopsy are considered in the evaluation for salvage therapy. In the absence of raised PSA, yield from imaging is negligible and not recommended.**(B/III)**

6.3 Radiotherapy

Experience in the last 3 decades has demonstrated that radiotherapy is effective in the permanent control of prostatic tumours.**(B/IIa)** However, as few patients undergo repeat biopsy of the gland to

confirm response, the true incidence of local control may be lower than the 65-88% reported.[71-76]

Long term results of radiotherapy in stage T1 and T2 patients are similar to those reported with radical prostatectomy despite differences in case selection and the lack of surgical staging of the lymph nodes in most cases. **(B/III)** The definition of endpoints needs to be considered in non-randomised comparisons.[77]

The late complications of radiotherapy include chronic mild-to moderate-cystitis (12.5%), diarrhoea (9.7%), proctitis (7.8%), rectal bleeding (4.4%), urethral stricture or bladder neck contracture (3%) and haematuria (3%). Severe complications are rare.[78,79]**(A/Ib)**

Pelvic nodal irradiation does not confer any benefit in terms of local control or survival.**(A/Ib)** Pelvic nodal involvement is invariably associated with the development of distant metastases.[80,81]

The data from trials (Annex 2) suggest a role for the use of concurrent hormonal therapy with radiation for the treatment of localised prostate cancer. However, the type of androgen deprivation and its duration remains to be established.[82-84] **(B/III)** Complications with radiotherapy for patients treated with neoadjuvant therapy may be lower.

Early reports have shown that 3-Dimensional Conformal Radiotherapy (3D-CRT) may improve local control and survival in patients with prostate cancer.[85,86] **(B/IIb)** Post high dose radiotherapy morbidity may also be limited by this approach.

Interstitial brachytherapy is generally not recommended for locally advanced disease: PSA > 10 ng/ml and high Gleason score.[87-90] **(B/IIa)** The morbidity includes substantial bladder toxicity such as dysuria, hematuria and other severe urinary symptoms. Forty-six percent of patients required medication to alleviate symptoms. Patients with significant pre-treatment lower urinary symptoms are especially at risk, with 14% exhibiting persistent severe urinary symptoms at 2 years after implantation. Five patients, early in the series, developed rectal ulcers. This effect was nearly completely eliminated with improved treatment plans. Of the 56 men who were

sexually potent prior to implantation, 86% retained potency at 3 years.[88-90] **(A/Ib)**

To assess for post-treatment disease status, PSA levels done 6-monthly for a period of 10 years and annually thereafter is recommended.[76,88,89,91] **(A/Ib)** Nadir PSA levels ($\leq$ 0.5 ng/ml), typically achieved at 12-24 months, is of prognostic significance for relapse.

6.4 Management of Locally Advanced Prostate Cancer (Stage T3 N0 M0, T4 N0 M0, T1-4 N1 M0)

In accordance to the TNM staging system, locally advanced disease would include T3:N0:M0, T4:N0:M0, and T1-4:N1:M0. There is evidence that long term survival is possible with control of locally advanced disease confined to the pelvis.[92,93] Endorectal coils for MRI may enhance imaging of the prostate.[94] **(B/III)**

Androgen deprivation improves survival of patients with locally advanced prostate cancer. Neoadjuvant hormonal therapy reduces the radiation field size and hence treatment-related morbidity.[82,83] **(B/III)** The role of adjuvant hormonal therapy for locally advanced prostate cancer is currently being evaluated. Preliminary findings showed no survival advantage but significant disease-free interval for patients who had immediate orchiectomy.[95]

For asymptomatic patients, surveillance is an option.

6.4.1 Treatment for locally advanced (T3) prostate cancer

While the mainstay of treatment is systemic androgen deprivation therapy, local therapy in the form of radical prostatectomy with adjuvant radiotherapy, hormonal treatment or radiotherapy with hormonal adjuvant therapy may offer some benefit.[96,97] **(B/III)**

Neoadjuvant hormonal therapy before radical prostatectomy is not recommended as there is no obvious benefit.[98] **(A/Ib)**

6.4.2 Treatment for locally advanced (N+) prostate cancer

Radiotherapy with hormonal therapy has been shown to achieve long-term survival but the extent of contribution from the local therapy remains unclear.[99]

Radical prostatectomy with adjuvant hormonal therapy is advocated by some who reported good long-term survival.[70,100-102]**(B/III)**

6.5 Biochemical failure

Biochemical failure is defined as serum PSA levels of 0.4 ng/ml following surgery, 0.5 ng/ml following radiotherapy, and/or 2 consecutive rising PSA values 3 months apart.**(B/IIb)** It is an elevation of, or consistently raised, PSA level after definitive treatment indicating persistent local or systemic disease. It usually precedes clinical recurrence by up to 3 years.[49,103,104]

Early elevated PSA levels in less than 12 months post-treatment may indicate distant spread of disease. The PSA level in this instance is also significantly higher than that in local recurrence. A short PSA doubling time or PSA velocity of more than 0.75 ng/ml/year may indicate systemic recurrence.[105,106]**(B/ III)** Elevated PSA levels more than 12 months post-treatment may indicate local recurrence.

Patients with biochemical failure need to be investigated for local or systemic recurrences.

- DRE is an unreliable early indicator of recurrence of local cancer following treatment.[107]**(B/III)**

- TRUS is of no value in the diagnosis of local disease after treatment when it is used independently. However, TRUS has a definite role in facilitating localisation and guiding systematic biopsy for patients with elevated PSA and/or suspicious DRE.[108-111]**(B/III)**

- Bone scan may be indicated to detect systemic bony metastasis although elevated PSA levels may precede positive bone scans by a median of 10 months.[107,112]

- CT/MRI of the abdomen and pelvis may be indicated in evaluating post-prostatectomy patients for adjuvant radiation with elevated PSA levels, normal bone scan, normal TRUS and biopsy.[113]**(B/III)**

- ProstaScint scan may enhance identification of systemic recurrence after treatment.[114]**(GPP)**

7 Treatment of metastatic prostate cancer (M1)

The presence of disease in non-pelvic lymph nodes, bone or distant (other than pelvis) sites constitutes the definition of M1/D2 disease. The presence of visceral or lytic metastatic lesions should alert clinicians of variant histology (e.g. neuroendocrine tumour).**(A/Ia)**

7.1 First line treatment

Hormonal therapy achieved favourable response in 75–80% of patients with advanced prostate cancer. The median duration of response is 18 months and the median survival time is 30/36 months. Early treatment improves local and distant disease control.**(B/Ib*)** The different treatment modalities – orchiectomy, luteinizing hormone-releasing hormone (LHRH) analogue and diethylstilbesterol (DES) – though differing in toxicity and costs, give equivalent results.[115-118] **(A/Ib)**

The Medical Research Council Trial (MRCT) in United Kingdom reported significant delay in disease progression with no survival difference in cases with stage M0 prostate cancer under hormonal therapy. A randomized study from the National Cancer Institute (NCI) reported that early androgen deprivation improves local and distant disease control with no survival benefits. A French study reported significant overall and disease-free survival favouring early LHRH treatment. Another large MRC randomized study on early vs deferred hormonal therapy reported improvement in local and distant disease control in stage M0 & M1 cases of prostate cancer with survival benefits only seen in the stage M0 group.[80,95,119,120]

However, early treatment exposes patients to longer duration of hormone-associated toxicity including osteoporosis, hot flushes, sexual dysfunction (decreased libido), gynaecomastia, nausea, vomiting, diarrhoea, insomnia and lethargy.[121]

* Although the trials reported are of higher level of evidence, the grade accorded is lower as the workgroup is of the opinion that more research in the area needs to be done.

Total androgen blockage (TAB) is not recommended presently.**(A/Ia)** Previous advocates of TAB – the US NCI intergroup 0036, the European Organization for Research and Treatment of Cancer (EORTC**)** phase III study and a Dutch study reporting significant progression-free survival benefits – have been refuted by recent studies and a large meta-analysis of 22 studies.[122-127] TAB may be indicated under some special circumstances:

- Flare prevention during first month of LHRH agonist therapy
- Severe symptoms, as faster relief is associated with initial TAB
- As second-line therapy[128,129]**(B/IIb)**

Intermittent androgen suppression is currently experimental,**(B/III)** although there are certain encouraging animal and phase II study results. It is associated with lower costs and improved quality of life (sense of well being, recovery of libido and potency). Currently, phase III trials are ongoing.[130-133]

Monotherapy with bicalutamide or finasteride is, at present, not recommended.**(A/Ib)**

7.2 Second line treatment

In Singapore, 50% of prostate cancer present as stage D2(M1) while only 24% of prostate cancer in USA present as such. Between 1989 and the mid 90s, the first-line treatment was castration (orchiectomy[134] or drug therapy with estrogen or LHRH agonist), anti-androgen or combined androgen blockade, (CAB – a combination of castration and anti-androgen). However, recent data suggests that CAB does not offer a significant survival advantage over castration alone (monotherapy). First line treatment, whether monotherapy or CAB, usually controls disease for only 12-18 months and second line treatment is very often necessary.[122,123,125,135] **(A/Ib)**

7.2.1 Definition

Treatment for prostate cancer patients with progressing disease through adequate primary hormonal therapy.

Progressing disease is defined by:

- an increase in size of measurable lesions, or the appearance of new measurable lesions; or
- an increase in PSA levels of at least 50% on at least 2 consecutive measurements, with a minimum period 2 weeks apart; or
- an increase in pain associated with new bony (non-measurable) lesions; or
- a combination of the above.

Adequate primary hormonal treatment is defined by the castration level of testosterone.

7.2.2 Overview of second line treatment of prostate cancer

Second line treatment of prostate cancer has not shown consistent survival advantage. Median survival is still less than 1 year following relapse. Palliation of symptoms is an important end-point. The selection of further treatment following relapse depends on many factors, including prior treatment, site of recurrence, coexistent illnesses and individual patient considerations. The absolute level of PSA at the initiation of therapy in hormone-refractory patients has not been shown to be of prognostic significance. The data on the predictive value of PSA changes (in patients on chemotherapy) for survival are conflicting.[136,137] None of the second line treatment options has shown consistent advantage. The choice of treatment should again be individualized. **(A/Ib)**

Problems associated with second line treatment trials include:

- Treatment endpoints in many earlier trials are not well defined e.g. stable disease (SD) has been regarded as evidence of response in some trials but not in others. Eighty-nine percent of so-called responses have been SDs. Most practitioners feel that SD is not a valid indicator of response in prostate cancer.

- A fall in PSA level is potentially confounding.[138,139] PSA decline correlates with measurable response in only 68% of the time. The decline may be due to a fall in rate of PSA gene expression, rather than loss of prostate cancer cells.

- Patients with no measurable disease are often excluded from trials, but patients with measurable disease (e.g. soft tissue lesions) may not be representative of prostate cancer as a group. Eighty to ninety percent of prostate cancer patients do not have measurable diseases.

- Documentation of the cause of deaths in elderly prostate cancer patients is not always reliable, given the presence of co-morbidity.

7.2.3 What is the preferred second-line treatment?

For patients who are using only LHRH agonist or oestrogen as primary therapy but whose testosterone level is not below castration level (defined as the limit of detection in individual laboratories), adding an anti-androgen is useful.**(GPP)**

Patients who are using only LHRH agonist or oestrogen as primary therapy but whose testosterone level is at castration level may benefit from indefinite use of LHRH agonist.**(B/III)**

For patients who are using anti-androgens or CAB, anti-androgen withdrawal is the preferred approach.**(B/IIa)** It may be useful to continue prescribing LHRH agonist indefinitely once it has been started even in relapse cases. However, data on this issue is conflicting.[140,141]

Anti-androgen withdrawal is mostly applied to flutamide and bicalutamide and is the preferred approach at relapse.[142] Although their response rates are similar, flutamide discontinuation leads to a much quicker appearance of response (days versus weeks). A 20% response rate can be expected from anti-androgen withdrawal, lasting

a median of 3.5 to 5 months (anecdotal cases of up to 2 years).[142,143] A prolonged period of flutamide usage is more likely to produce favourable withdrawal response.

The withdrawal benefits of megestrol acetate, a progesterone agent which acts centrally as well as at the androgen receptor, has also been reported.[144]**(B/IIb)**

7.2.4 Other treatment options

Beyond the measures described in the previous section, the following options have been used although there is insufficient data to guide the choice among them.

Addition of a second anti-androgen

Changing to bicalutamide after failure of flutamide therapy has been shown to produce a 20% response rate and the effect is dose-dependent – 150-200 mg daily being preferred to 50 mg. However, flutamide for bicalutamide failure has not been evaluated.[145]

Adrenal androgen inhibitors

- *Aminoglutethimide (250 mg po tid) + replacement hydrocortisone*

  A review of 13 randomised trials showed 9% objective response rate. The adverse effects include fatigue, rashes, orthostatic hypotension and ataxia.[144]

- *Aminoglutethimide + replacement hydrocortisone + flutamide withdrawal*

  This has been shown to produce responses in heavily-pretreated patients.[146] Ketoconazole can produce a 15% objective response and 78% PSA response at 400 mg po tid + replacement hydrocortisone. Ketoconazole 200 mg tid has been documented to produce similar results with no replacement hydrocortisone. The medication is taken with an empty stomach as low pH promotes absorption.[143,147]

Supportive care with prednisolone

Low-dose glucocorticoids (e.g. prednisolone 10 mg daily) are effective and achieve reasonable palliative relief for patients who are not fit for aggressive chemotherapy.[148] **(A/Ib)** Low-dose prednisolone is probably as effective as the addition of flutamide as a second-line therapy.[149] **(B/IIa)**

Chemotherapy or chemo-hormonal therapy

Before 1991, the response rate of chemotherapy ranges from 4.5-8.7%.[150,151] New drugs, drug combinations with more potent anti-emetics and the use of PSA levels as a monitoring tool have led to renewed interest in chemotherapy in the 1990s. Many new clinical trials are currently underway.

- *Mitoxantrone + prednisolone (M+P)*

  M+P combination is USFDA (United States, Food and Drug Administration) approved. In a Canadian trial, it produced a 29% response rate with palliation of pain as the endpoint, as well as a longer duration of palliation. The result was better than that of using prednisolone alone (12% response rate with similar endpoint). The survival benefit was possibly due to a cross-over design.[148] **(B/Ib*)**

- *Estramustine + estramustine-based combinations*

  Estramustine binds to microtubule-associated proteins.
  - Oral estramustine alone produced 19% objective response rate in 18 phase II trials.
  - Estramustine (10-15 mg/kg po daily) + vinblastine (3-4 mg/m^2 IV weekly) produced 40% objective response rate and 54% PSA response in phase II studies. Estramustine +

* Although the trial reported is of a higher level of evidence, the grade accorded is lower as the workgroup is of the opinion that more research in the area needs to be done.

vinblastine combination was superior to vinblastine alone in a phase III study.[125,152-155] **(B/IIb)**

- Estramustine (15 mg/kg po daily) + etoposide (50 mg/m^2 po daily) for 21 days out of 28 days is an active combination**.**[156]
- *Estramustine + paclitaxel (120 mg/m^2 over 96 hours) combination every 21 days. Two drugs that impair microtubule function by complementary mechanisms.*[154]

Other chemotherapeutic agents

Doxorubicin (20 mg/m^2 IV weekly) produced a 16% objective response. Doxorubicin (20 mg/m^2 weekly) + ketoconazole (400 mg po tid) for 6 weeks, rest 2 weeks, produced a 58% objective response and a 55% PSA response. Doxorubicin + ketoconazole alternating with estramustine + vinblastine produced a 75% objective response that lasted 8.4 months, with an overall survival of 19 months. Estramustine + weekly doxorubicin produced a 45% objective response, a 58% PSA response and a 27% subjective response. Estramustine + etoposide + cisplatin (or carboplatin) produced an objective response of 61%.[157-160]

Suramin in hormone refractory prostate cancer

Suramin inhibits PDGF, TGF-beta and other growth factors. In phase II studies, it produced a 20% PSA response. However, negative studies have also been reported. Toxicities included polyradiculopathy, myelopathy, coagulopathy and vortex keratopathy. A phase III multicentre study reported significant palliative advantage and delayed disease progression.[136,161-165]

7.3 Treatment for bone pain

7.3.1 Radiotherapy

- External beam irradiation is indicated for painful bony metastases, or unstable bony metastases.
- Hemibody irradiation is indicated for patients who have too many symptomatic bony metastases to be treated individually.
- Radioisotopes such as Strontium-89 and Samarium-153 are beta-emitting isotopes which can improve bone pain in up to 70% of treated patients. However, this may cause myelosuppression, especially if chemotherapy is subsequently needed.[166]

7.3.2 Bisphosphonates

Bisphosphonates can reduce bone pain in up to 76% of treated patients.[167] **(B/IIb)**

7.3.3 Pain service

The availability of a pain service to co-ordinate the use of oral and intravenous analgesics and opiates is encouraged.

8 Clinical audit

Assessing treatment responses

Given the different treatment endpoints in prostate cancer, it is necessary to report and analyse treatment data based on individual endpoints. [168] Accepted treatment endpoints in prostate cancer are:

For metastatic disease:

i. objective response of measurable disease;
ii. PSA response; and
iii. subjective response

For local-regional disease:

i progression-free survival;
ii disease-specific survival; and
iii overall survival.

One of the most robust treatment endpoints in prostate cancer is survival. In this regard, the overall survival is probably more reliable than disease-specific survival since documentation of the cause of deaths in prostate cancer is often not reliable.

9 Recommendations for research

There is an urgent need for good research on early detection methods that is focused on Asians to direct future programs in disease control. Randomised control trials to compare radiotherapy with observation should be carried out. Improvement in techniques to minimize morbidity and improve curative rates should be explored. Most of the data quoted are from Western literature; there is a paucity of well-designed Asian studies. As the epidemiology of prostate cancer is very geographically dependent, studies focusing on the differences may eventually shed light on the aetiology and natural history of this disease.

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Annex 1 TNM staging of prostate cancer

(Union Internationale Contre le Cancer – American Joint Committee on Cancer – UICC-AJCC)

Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor not palpable or visible by imaging
T1a	Tumor incidental histologic finding in 5% or less of tissue resected or of Gleason score not more than 5
T1b	Tumor incidental histologic finding in more than 5% of tissue resected or of Gleason score more than 5
T1c	Tumor identified by needle biopsy (e.g. because of elevated PSA)
T2	Tumor confined within prostate*
T2a	Tumor involves half of a lobe or less
T2b	Tumor involves more than half of a lobe but not both lobes
T2c	Tumour involves both lobes
T3	Tumor extends through the prostatic capsule**
T3a	Unilateral extracapsular extension
T3b	Bilateral extracapsular extension
T3c	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles and/or pelvic wall

*Note:	Tumor found in 1 or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.
**Note:	Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.

Regional lymph nodes (N)

Regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries. They include the following groups (laterality does not affect the N classification): pelvic (NOS), hypogastric, obturator, iliac (internal, external, NOS), periprostatic, and sacral (lateral, presacral, promontory {Gerota's}, or NOS).

Distant lymph nodes are outside the confines of the true pelvis and their involvement constitutes distant metastasis. They can be imaged using ultrasound, computed tomography, magnetic resonance imaging, or lymphangiography, and include: aortic (para-aortic, periaortic, lumbar), common iliac, inguinal, superficial inguinal (femoral), supraclavicular, cervical, scalene, and retroperitoneal (NOS) nodes.

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node or nodes

Abbreviation: NOS, not otherwise specified.

Distant metastasis*** (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

***Note: When more than 1 site of metastasis is present, the most advanced category (pM1c) is used.

Histopathologic grade (G)

The Gleason classification scheme is currently the most commonly used system. Low power magnification is used to assess the glandular pattern of the tumour and the relationship to the stromal compartment. Five tumour grades progressing from the most (1) to the least (5) differentiated are recognised. The final grade assigned the tumour is a sum of the grade of the five tumour patterns that constitute the largest and next largest tumour mass.

Gleason 2-4	-	well differentiated
Gleason 5-7	-	moderately differentiated
Gleason 8-10	-	poorly differentiated

Annex 2 Results of conventional external beam radiotherapy

Results of conventional external beam radiotherapy in Stage T1 to T3 carcinoma of the prostate (from De Vita 5th edition)

Author	Stage	Patients	Survival rate (%)			Local relapse-free survival rate (%)		
			5 year	10 year	15 year	5 year	10 year	15 year
Bagshaw	T1	335	85	65	40	90	85	90
	T2	242	83	55	35	80	70	65
	T3	409	68	38	20	76	63	40
Hanks	T1	60	84	54	51	96	96	83
	T2	312	74	43	22	83	71	65
	T3	216	56	32	23	70	65	60
Zagars	T1	32	76	68	-	100	100	-
	T2	82	93	70	-	97	88	-
	T3	551	72	47	27	88	81	75
Perez	T1	48	85	70	-	90	80	-
	T2	252	82	65	-	85	76	-
	T3	412	65	42	-	72	60	-

Workgroup members

The members of the workgroup are:

Chairman:	Dr Christopher Cheng
Members:	Dr Christopher Chee Dr Chia Sing Joo Dr Kong Hwai Loong Dr Lewis Liew Dr Robert Lim Dr Ng Foo Cheong Dr Ng Lay Guat Dr Damian Png Dr Terence Tan Dr Tan Puay Hoon Dr Tan Yeh Hong Dr Toh Khai Lee Dr Karmen Wong Dr Yang Tuck Loong Dr Sidney Yip