National Medicines Information Centre

VOLUME 18
NUMBER 5
2012

ST. JAMES'S HOSPITAL • DUBLIN 8
TEL 01-4730589 or 1850-727-727 • FAX 01-4730596 • www.nmic.ie

PROSTATE CANCER

- **Prostate cancer is the most frequently diagnosed male cancer accounting for 30% of all newly diagnosed cancers in males in Ireland with a five-year survival of 88%**
- **Management involves a multidisciplinary approach with input from primary care, radiology, pathology, urology, radiation oncology and medical oncology**
- **There are multiple therapeutic options with no consensus on optimum therapy**
- **Proactive management of treatment-related toxicities is an integral part of prostate cancer treatment**

INTRODUCTION

Prostate cancer is the most common male cancer in the developed world, second only to lung cancer worldwide, and is the sixth most common cause of cancer death among men.[1] This is a disease of increasing age (autopsy studies have noted up to 70% of men >80 years have asymptomatic disease) and high survival figures.[2,3] In Ireland, prostate cancer accounted for 30% of all diagnosed invasive cancers during 2007-9 and 13% of deaths.[4] The median age at diagnosis is 69 years. Although the incidence of prostate cancer in Ireland ranked highest of all 30 European countries during 2008, mortality rates were ranked 11th highest;[4] the discrepancy is related to the use of prostate-specific antigen (PSA) testing. This bulletin will outline the diagnosis and management of prostate cancer.

RISK FACTORS FOR PROSTATE CANCER

Increasing age is the most important risk factor for prostate cancer.[2] In Ireland, the majority of cases are detected in men aged 65-84 years with 37% detected in men <65 years of age.[4] **Family history** is important; men with a brother or father diagnosed with prostate cancer at 50 years, have an approximately 2-fold increased risk of prostate cancer; this rises to an 8-fold risk with >2 first degree relatives.[3] **Sub-Saharan African ancestry** is a risk factor, while Asian men have much lower rates of prostate cancer.[1] It is not clear whether this is due to ethnic genetic differences, environmental differences or both. While some epidemiologic studies have reported an association between benign prostatic hyperplasia (BPH) and prostate cancer, a 7-year prospective study showed **no significant association between symptomatic BPH and prostate cancer risk.**[5]

Studies have shown increased risk associated with **various dietary intakes** including high levels of high-saturated fats and red meats and reduced intake of fish, fruit and vegetables (e.g. tomatoes).[3,6] **Obesity** has been associated with higher-grade cancers, possibly as a result of altered hormone levels. The **number of sexual partners** may be a risk factor, possibly due to infection / inflammation.[3]

PRESENTATION AND DIAGNOSIS OF PROSTATE CANCER

Presentation: Men may present **asymptomatically** (i.e. an abnormal PSA result) or with symptoms relating to the primary tumour (i.e. **prostatic/ local symptoms**) or less commonly with symptoms related to **metastatic disease** (e.g. pathological fracture, hypercalcaemia, anaemia).[2] Local symptoms may include symptoms of bladder outlet obstruction such as nocturia, hesitancy or pain on passing urine, incomplete emptying and a diminished urinary stream; in many cases these reflect benign conditions such as BPH rather than malignancy.[3,7] However, these symptoms should prompt examination to rule out prostate cancer.

Diagnosis of prostate cancer involves (1) clinical evaluation i.e. digital rectal examination (DRE), (2) evaluation of plasma PSA and, if indicated, (3) prostate biopsy.[7]

DRE: Most prostate cancers arise in the peripheral zone near the capsule of the prostate, which is the area palpable by DRE.[3] The size and contour of the prostate gland can be determined by DRE and any palpable abnormality should be pursued;[7] **25-50% of DRE abnormal findings prove to be prostate cancer.** Although not uniformly accurate, DRE may provide evidence of a cancer's size and pathologic stage and in some cases may correlate with prognosis. The size and location may also provide information when deciding on the modality of treatment.[3]

PSA is produced by the prostatic secretory cells (though not exclusively so) and is normally released into the blood as a consequence of disruption of normal prostate architecture.[8,9] Originally used to monitor response to treatment in patients with prostate cancer, PSA monitoring was found to have some benefit as a diagnostic marker.[10] Large studies have demonstrated that almost 70% of cancer cases can be detected using the internationally recognised cut-off PSA level of > 4ng/ml.[3] **Elevated PSA is not specific for malignancy** as BPH, prostatitis and increasing age also lead to elevated levels.[1,11] Conversely, a **normal PSA does not rule out prostate cancer**. Among a group of almost 3,000 men who had normal DRE and PSA levels of ≤ 4 ng/ml, prostate cancer, including high-grade cancers, was detected on biopsy at all levels of PSA during a 7-year follow-up (Table 1).[10]

Table 1: Risk of prostate cancer in relation to PSA values* in low - normal range[10,11]

PSA level (ng/ml)	0 – 0.5	0.6 – 1	1.1 – 2	2.1 – 3	3.1 – 4
Risk of Prostate Cancer (%)	6.6	10.1	17.0	23.9	26.9

*internationally recognised cut-off PSA level ≤ 4 ng/ml

PSA screening for prostate cancer has been evaluated in men, aged 55-69 years, in 2 large long-term randomised controlled trials, with **conflicting results**.[13,14] A European study randomised 162,000 men to PSA screening every 4 years vs. no screening. During a median follow-up of 9 years, PSA screening showed a benefit in terms of reduced rates of prostate cancer death (but not overall mortality) of 20% but was associated with high rates of over-diagnosis.[13] Follow-up at 11 years confirmed the initial findings[14] and noted that any benefit seen might be offset by reduced quality of life (due to treatment).[15] A US study randomised 76,000 men to annual PSA screening for 6 years plus DRE for 4 years vs. no screening. After 7-10 years' follow-up, there was no benefit in terms of reduction in the rate of prostate cancer associated with PSA screening.[16] However, the overall mortality in this

study was low and many of the control group had undergone independent PSA/DRE examination.

National PSA screening is not recommended in any country, due to a lack of definitive information on its benefit/risk. **Men should be counselled about the implications of a positive result prior to PSA testing** (see national guidelines below).[11] There are conflicting views as to the usefulness of measuring PSA velocity, PSA doubling time or percent free PSA compared with standard (i.e. total) PSA levels.[12,17] Early urinary biomarker prostate cancer antigen 3 (PCA3) may be useful in improving diagnostic accuracy but it is not yet widely available.[18,19]

Prostate biopsy is the standard way to obtain tissue to confirm the presence of prostate cancer.[12] It is performed, under antibiotic cover, using transrectal ultrasound (TRUS) guidance. The decision to refer a patient for prostate biopsy is determined on the basis of the PSA parameters ± a suspicious DRE as well as other factors, such as patient co-morbidities, age (and expected life expectancy) and therapeutic consequences; the **patient must be involved in the final decision**.[20] A minimum of eight cores are obtained usually, each of which is graded. Once cancer has been confirmed, the decision to proceed with further staging workup is guided by which treatment options are available to the individual patient, taking into account his age, co-morbidity and preferences.[12,17]

Histology: The majority (> 95%) of prostate cancers are adenocarcinomas.[9] Primary prostate tumours often contain multiple independent histologic foci.[3,9] Each tumour is graded according to the **Gleason score**. This evaluates the degree of differentiation seen in the cancer from 1 (well differentiated) to 5 (poorly differentiated) and is commonly reported as 2 separate numbers (i.e. 3 + 4) referring to the degree of differentiation within the 2 most prevalent areas of cancer from the core biopsies. The Gleason score is also used for prognostic purposes.[3] Table 2 outlines the different clinical stages of prostate cancer.

Table 2: Different clinical stages of prostate cancer[21,22]

Stage	Description
Stage I *(local)*	Tumour is localised to one lobe of prostate
Stage II *(local)*	Tumour is found in both lobes of prostate but is contained within the prostate capsule
Stage III *(locally advanced)*	Tumour has spread locally (through the capsule) but has not spread to lymph nodes or elsewhere in body
Stage IV *(metastatic)*	Tumour has invaded adjacent structures and/or there is evidence of metastatic spread

MANAGEMENT OF PROSTATE CANCER

Current management of prostate cancer involves a multidisciplinary approach with input from primary care, radiology, pathology, urology, radiation oncology and medical oncology. Management depends on the presentation of prostate cancer: early / localised cancer, locally advanced cancer, biochemical failure (rising PSA in the absence of metastatic disease), hormone-sensitive metastatic disease and hormone-refractory metastatic disease. **There are multiple therapeutic options for most phases of the illness with no consensus on optimum therapy.**[17,22]

LOCALISED PROSTATE CANCER

The majority of primary prostate cancers are localised at time of diagnosis.[12,23] **Localised prostate cancer is categorised as low, intermediate or high risk**, based on the (1) number of positive cores, (2) Gleason score and (3) PSA levels. This risk classification is used to decide treatment and also has prognostic value.[17] Radiographic investigations (i.e. CT / MRI / bone scans) are usually considered for those with high risk disease, although bone scan may be indicated in a patient with intermediate risk disease if there is suspicion of bone metastases.[17] Table 3 summarises treatment options for men with localised prostate cancer.

Table 3: Treatment options for recently diagnosed localised prostate cancer[17,22]

Modality	Low risk*	Intermediate risk*	High risk*
Active surveillance	Preferred option	Option	Not an option
Watchful waiting**	Option	Option	Option
Prostatectomy (RP)	Option	Preferred option	Preferred option***
Radiotherapy / Brachytherapy (RT)	Option	Preferred option	Preferred option***

* Risk calculation based on number of positive biopsy cores, Gleason score, PSA levels
** Suitable only for patients who are not candidates for curative radical therapy
***Only if there is a realistic prospect of long-term disease control; neoadjuvant androgen deprivation therapy usually co-prescribed with RT

Active surveillance with ***selective delayed intervention*** (AS) describes the management, often recommended for patients with **localised low-risk prostate cancer.**[3] It involves active monitoring (DRE and PSA every 6 months and TRUS biopsy every 12 months or as required) until evidence of progression is suspected at which time patients are re-evaluated and appropriate intervention(s) implemented. It aims to reduce the ratio of overtreatment in low-risk prostate cancer patients, who may be suitable for curative therapy and is based on data demonstrating that such patients have a 20-year prostate-specific survival rate of 80-90%.[12] **Watchful waiting** (WW) involves following patients until they develop evidence of symptomatic disease progression, at which time therapy, usually androgen deprivation therapy (ADT) is introduced.[12] WW is different from AS because the **goal of WW is to limit morbidity** from the disease and therapy.[12] WW may be considered the most appropriate option depending on the age, general status and life-expectancy of the patient.

Surgery: Radical prostatectomy (RP) involves removal of the entire prostate gland ± pelvic lymphadenectomy. RP may be indicated for intermediate and high risk localised prostate cancer.[22] Complications include incontinence, infertility and impotence, the frequency of which is determined by the extent of the surgical procedure.[12,17] Before the widespread use of PSA testing, RP was shown to prolong survival in patients with intermediate-risk localised prostate cancer compared with observation during a median 12-year follow up, especially in patients < 65 years.[24] A more recent study, carried out in the era of PSA testing, has shown no significant reduction in prostate cancer death or all-cause related mortality for RP compared with observation, except for patients with PSA levels > 10ng/ml.[25] The study involved patients with local disease (66% had intermediate or high risk disease) and the **surgery group had a higher rate of incontinence and erectile dysfunction compared with the control groups** (17 vs. 6% and 81 vs. 44% respectively).

Radiotherapy: There are a number of radiotherapy (RT) techniques in current use. External beam radiotherapy **(EBRT)** is the current standard RT in prostate cancer.[12,17] Compared to RP, it is non- or minimally invasive and therefore less likely to cause urinary incontinence.[26] Observational data suggest that long-term disease control with RT is similar to that seen with RP. Radiation dose escalation has been shown to improve survival. RT may be used as definitive treatment or as an adjunct, following RP in patients with high-risk disease. Similarly, patients with high-risk disease may receive combined RT and ADT to improve survival.[3,12,22] Complications include acute radiation cystitis, urethritis, acute radiation proctitis (with tenesmus and pain); late effects include impotence in up to 50% and rectal bleeding.[2] **Brachytherapy** involves the insertion of radioactive pellets (I-123; or palladium-103) directly into the prostate gland.[26] These have been shown to produce biochemical tumour control (i.e. in terms of PSA) and are associated with high survival outcomes in patients with low-risk disease. Side effects include urinary symptoms such as temporary incontinence and radiation proctitis and late onset urethral strictures; impotence is thought to occur less frequently than with EBRT.[2] Brachytherapy may be combined with EBRT for high risk patients with localised disease.[3,22]

Androgen deprivation therapy (ADT): Most prostate cancers are hormone (testosterone) dependent and are therefore sensitive to ADT.[21] This can be induced surgically (bilateral orchiectomy) or medically (by the use of various hormonal agents, which decrease the level of testosterone to castrate levels).[27] For patients with localised prostate cancer of intermediate ± high risk, (neo)adjuvant medical ADT may be used in conjunction with RT (i.e. administered before, during and for 3-9 months after RT – see Table 3). Monotherapy with ADT is not usually recommended for patients with local disease, unless they are unsuitable for radical therapy.[12] The currently available hormonal therapies are described in the next section.

LOCALLY ADVANCED PROSTATE CANCER

Locally advanced prostate cancer covers a spectrum of disease from a tumour that has just spread through the capsule to large cancers invading several local structures.[22] Treatment options may involve (a) radiotherapy (RT) with (neo)adjuvant hormonal therapy or (b) hormonal therapy alone.

Hormonal therapy: More than 80% of men with locally advanced prostate cancer respond to ADT using hormonal therapies.[28] Table 4 outlines the various ADT currently used for the treatment of prostate cancer.

Table 4: Androgen deprivation therapies (ADT) used in hormone-dependent prostate cancer[29-37]

Drug Class	Mode of Action (MoA)	Administration Points	Precautions for Use
GnRH analogues Buserelin Goserelin Histrelin Leuprorelin Triptorelin	Inhibits pituitary LH and FSH secretion by down regulation of receptors → suppression of testicular function with chronic administration. Hormonal suppression apparent within 4-6 weeks.	S/C or I/M administration at 1, 2, 3, 6 or 12 month intervals, depending on formulation. (buserelin also available as nasal spray, 6/day administrations)	May see initial ↑ levels of testosterone therefore co-administration of anti-androgen is recommended for first 3-4 weeks. ADRs: hot flushes, sexual dysfunction, ↑ adiposity; risk of osteoporosis, anaemia, DM, CVD with long-term use.
Anti-androgens Bicalutamide Flutamide Cyproterone acetate*	Androgen receptor antagonists	Oral preparations used in combination with GnRH analogues / surgical castration. Used before and during GnRH analogue therapy X 3-4 weeks.	ADRs : gynaecomastia, hot flushes, anaemia, GI upset, hepato-biliary disorders.
GnRH antagonists Degarelix	Binds GnRH receptors in pituitary → ↓ secretion of LH and FSH → ↓ testosterone from testes.	S/C at monthly intervals after an initial loading dose.	ADRs : hot flushes, anaemia, gynaecomastia, sexual dysfunction, injection site reactions, risk of osteoporosis.

*used for management of tumour flare at the start of GnRH analogue therapy
GnRH = gonadotrophin releasing-hormone; LH= luteinising hormone; FSH= follicular stimulating hormone; DM= diabetes mellitus; CVD = cardiovascular disease; ADRs = adverse drug reactions. See the individual Summary of Product Characteristics for full prescribing information

Gonadotrophin releasing-hormone (GnRH) analogues suppress testicular function by inhibiting LH and FSH secretion from the pituitary (Table 4). **Initial treatment may result in a "disease flare"** i.e. initial rise in LH leading to increased levels of testosterone and temporary deterioration in the patient's status.[29-33] This is prevented by the use of an anti-androgen (usually cyproterone acetate) starting 3-5 days before start of treatment and continued until testosterone levels have reached optimum levels (usually 3-4 weeks in total). Guidelines recommend use of GnRH analogues for at least 2 years, especially if combined with RT, and depending on patient status;[27] toxicity seen with longer-term usage (Table 4) reflects chronic testosterone deprivation.

Anti-androgens act as competitive androgen receptor antagonists. **They are usually administered in combination** with GnRH analogues or surgical castration.[34,35] If they are used as monotherapy, testosterone levels may rise (due to androgen blockade in the hypothalamic and pituitary glands).[3] Their toxicity profile is outlined in Table 4.

GnRH antagonists reduce production of testicular testosterone by directly inhibiting LH and FSH secretion (Table 4). Because of the mechanism of action, **these agents are not associated with an initial disease flare**.[36] Studies have shown testosterone suppression similar to leuprorelin during 12 months of treatment with degarelix.[36]

Continuous vs. intermittent ADT: As outlined in Table 4, ADT may be associated with considerable toxicity. Recent clinical studies have suggested that intermittent ADT administration may result in similar falls of testosterone compared with continuous administration but with an improved quality of life and may also be associated with a delay in developing **castration-resistant prostate cancer (i.e. evidence of progression, despite low testosterone levels - CRPC)**.[28,38] Definitive evidence is awaited.

Hormonal therapy resistance: While ADT is noncurative, it slows disease progression, enhances quality of life and may be associated with modest increases in survival.[27] For those who respond to ADT, the **median time to progression to CRPC is 18-30 months.**[27]

CASTRATION-RESISTANT PROSTATE CANCER

Nowadays, CRPC is usually detected as **biochemical failure i.e. rising PSA, with no evidence of metastases.**[3] The treatment plan for CRPC depends on whether the patient is symptomatic or asymptomatic, their general status, age and preference for treatment options.

Hormonal therapy: All patients who develop CRPC while on ADT should have continued androgen suppression; each additional hormonal manipulation is estimated to produce a decline in PSA levels for a median of 3-5 months.[3] This may be the only treatment indicated in asymptomatic cases. A meta-analysis of 27 trials has shown a small survival advantage with **maximal androgen blockade**, i.e. GnRH analogue therapy plus anti-androgen / orchiectomy, compared with ADT monotherapy.[17] Further options include (1) **oestrogen therapy** which can lead to responses of 20-40%; however, its toxicity profile includes gynaecomastia, GI toxicity and thromboembolic disease, (2) **ketoconazole** (unlicensed indication) which is thought to act by inhibiting adrenal production of testosterone; caution with its use is urged because it is a powerful inhibitor of CYP3A4 and (3) **low dose corticosteroids** (e.g. prednisolone) which decrease adrenal function (including the production of androgens) and may be used following failure of second-line hormonal therapy.[3]

METASTATIC PROSTATE CANCER

Patients may develop metastatic prostate cancer many years after initial therapy or may present with metastatic disease. The goals of managing patients with metastatic disease are to (1) control symptoms, (2) maintain quality of life and (3) prolong survival.

Hormonal therapy: ADT is recommended for all patients; hormonal manipulations as described previously are used as initial management for metastatic prostate cancer; the regimen used depends on whether the patient has CRPC or not.[3,17] The initial flare seen with GnRH analogues must be carefully managed in these patients.[29-33] Corticosteroids may also contribute to palliation of painful disease, if present in these patients.[3,17]

Chemotherapy: Docetaxel, in combination with prednisolone has been shown to prolong life and improve pain control in symptomatic patients with evidence of metastatic spread.[39] Toxicity includes alopecia, GI toxicity (nausea, vomiting, and diarrhoea), sensory neuropathies, bone marrow suppression and cardiovascular disease. Therefore, its use is limited to patients with a good performance status.[22]

New agents: A number of new agents, some with novel modes of action, have been developed in recent years with clinical trials demonstrating survival benefit. **Abiraterone** inhibits the enzyme CYP17 which is required for androgen biosynthesis in the testes, adrenal glands and prostate cancer tissue.[40] In a study of metastatic CRPC patients, previously treated with docetaxel, abiraterone improved survival and reduced pain and fractures when added to GnRH analogues and prednisolone therapy.[41] Toxicity included mineralcorticoid toxicities (hypokalaemia, fluid retention). The National Cancer Control Programme (NCCP) has recently granted approval for its use in patients who have progressive metastatic disease following chemotherapy.[42] **Cabazitaxel** has recently been licensed for use in patients with metastatic CRPC.[43] It is from the same class as docetaxel and clinical studies have shown survival benefit in patients whose disease had progressed after docetaxel; toxicity profile is similar to that of docetaxel.[43,44] Other **novel agents** currently under clinical investigation for metastatic prostatic cancer include the alpha-particle emitting nuclide, **radium-223**, the dendritic cell vaccine **sipuleucel-T** and the anti-androgen **enzalutamide**.[44,45] It is hoped that newer therapies will result in improved survival in patients with advanced prostate cancer in the future.

Symptom management is tailored to the individual patient's disease. Options include analgesia and localised radiotherapy (for bony lesions) and surgery (to manage adverse effects of tumour masses e.g. obstructive uropathy). Radiopharmaceuticals such as **strontium-89** may help with refractory bony pain, especially if the patient is not suitable for chemotherapy.[22,44] Bisphosphonates or denosumab may be considered for the prevention and management of skeletal-related events, (pathological fracture, spinal cord compression, refractory pain and hypercalcaemia) secondary to bony metastases.[20,44]

MANAGING TREATMENT-RELATED TOXICITY

Several of the treatment options for prostate cancer are associated with significant long-term sequelae. **Patients and their partners should be counselled about the benefits and risks of each treatment option, prior to its implementation.** Table 5 outlines the most frequently seen treatment-related toxicities and their management.[22]

Table 5: Treatment-related toxicities and their management in patients with prostate cancer[22]

Treatment modality	Expected toxicity	Management options
All treatments	Sexual dysfunction / infertility Fatigue	Referral to erectile dysfunction services; offer sperm storage Recommend exercise programmes to improve wellbeing
Radical prostatectomy / Radiotherapy	Damage to structures in pelvis / urinary / GI tract	Referral to specialist urology / GI services
GnRH analogues / GnRH antagonists	Hot flushes Osteoporosis Obesity / chronic disease	Intermittent progestogens Bisphosphonates once diagnosed (not used prophylactically) Proactive management once diagnosed
Anti-androgens	Gynaecomastia Hot flushes Osteoporosis	Prophylactic radiotherapy to breast buds Intermittent progestogens Bisphosphonates once diagnosed (not used prophylactically)

All treatments may result in reduction or loss of sexual function and infertility, which may remain after completion of treatment, therefore a plan for dealing with this possibility must be discussed and agreed with the patient.[20] The risk of structural damage associated with surgery or radiotherapy also requires ongoing surveillance.

FOLLOW-UP OF PATIENTS

Review: After completion of treatment, patients should be followed up by review, clinical examination and assessment of PSA levels; this should occur (no sooner than 6 weeks post treatment completion) at 6 monthly intervals for 2 years and yearly thereafter.[20,21] DRE is not indicated if PSA levels are stable. Follow-up also involves management of treatment-related toxicities (sexual dysfunction, GI enteropathy, urinary incontinence or urethral stricture).[21]

Recurrence: If evidence of recurrence is identified, the treatment pathway depends on the extent of the cancer (local recurrence, biochemical failure or metastases) and presence / not of symptoms, as well as patient status, age, ongoing treatment-related toxicity and preferences in terms of further management options. Asymptomatic patients may have treatment deferred until clinical symptoms occur. [22]

Cancer survivorship: As a consequence of the cancer and its treatment, return to normal life may not be easy for some patients. Patients should be encouraged to undertake regular physical activity, adopt a healthy lifestyle and avoid weight gain, each of which can worsen performance status.[21] The Irish Cancer Society has a series of practical services, including counselling, for cancer survivors and their partners (http://www.cancer.ie/how-we-can-help)

NATIONAL REFERRAL GUIDELINES FOR SUSPECTED PROSTATE CANCER: SUMMARY

The National Cancer Control Programme (NCCP) has published prostate cancer referral guidelines for GPs.[11,48] These guidelines are summarised as follows:

- Males, aged 50-70 years (or 40-70 years if first degree relative with prostate cancer ***or*** of African ethnicity) who present with lower urinary tract (UT) symptoms or unexplained back pain should undergo assessment (including urinalysis, creatinine, haemoglobin, DRE and PSA).
- **PSA testing should only be carried out after full advice and provision of information, as to the potential implications of a positive result** [patient information leaflets are available from NCCP at www.cancercontrol.hse.ie].
- Any patient who presents with an abnormal DRE should be referred to a urologist regardless of PSA results.
- If the PSA test is abnormal (check local PSA reference range), it should be repeated after 6 weeks before referral as results can vary by 30%.
- Delay PSA testing by 6 weeks if subject has active UT infection, prostatitis, or is post-prostate biopsy / TURP.
- PSA laboratory result will need to be adjusted (doubled) if patient is on finasteride / dutasteride (interference with laboratory test).
- DRE performed before the PSA analysis does not raise the result.
- **Patients with abnormal findings** (abnormal hard prostate on DRE or second abnormal PSA at 6 weeks after an initial abnormal PSA test) **can be referred via the National Rapid Access Prostate Clinic Referral Form** to one of the 8 national rapid access prostate clinics.

The full guideline and copies of the rapid access prostate clinic referral form are available to download at:
http://www.hse.ie/eng/services/Find_a_Service/National_Cancer_Control_Programme/Health_Professional_Information/

List of references available on request. Date of preparation: November 2012

References for Prostate Cancer NMIC Bulletin Volume 18 No5 2012

1. Baade P et al, International epidemiology of prostate cancer: geographical distribution and secular trends. Mol. Nutr. Food Res. 2009; 53: 171-84

2. Genitourinary Cancers *in* Oxford Handbook of Oncology, third edition. Eds: Cassidy J, Bissett D, Spence R, Payne M. Publishers Oxford University Press. UK 2010. pgs 400-9

3. Zelefsky M et al, Cancer of the Prostate *in* DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology, 9th Edition, Pubs: Lippincott, Wilkins and Williams, 2011. Pgs 1220-1235

4. NCRI Annual report 2011.Available at www.ncri.ie. Accessed 19th November 2012

5. Schenk J et al, Association of symptomatic benign prostatic hyperplasia and prostate cancer: results from the prostate cancer prevention trial. Am J epidemiol 2011; 173: 1419-28

6. Nelson W et al, Prostate Cancer: mechanisms of disease. NEJM 2002; 349: 366-81

7. Gavin A and McElwee G, Common Cancers in Irish men, Modern Medicine 2012; 42(5): 38-41

8. Filella X et al. Value of PSA (prostate specific antigen) in the detection of prostate cancer in patients with urological symptoms. Results of a multicentre study Eur J Cancer 1996; 32A: 1125-8

9. Shen M and Abate-Shen C. Molecular genetics of prostate cancer: new prospects for old challenges. Genes & Devel 2012; 24: 1967-200

10. Thompson I et al, Prevalence of prostate cancer among men with a Prostate-Specific Antigen level ≤4.0ng/ml. NEJM 2004; 350: 2239-46

11. National Prostate Cancer GP Referral Guidelines. National Cancer Control Programme. Available for download at: http://www.hse.ie/eng/services/Find_a_Service/National_Cancer_Control_Programme/Health_Professional_Information/Prostate_Referral_Guideline.pdf. Accessed 22nd November 2012

12. Heidenreich A et al, EAU guidelines on prostate cancer. Part 1: screening, diagnosis and treatment of clinically localised disease. Eur Urol 2011; 59: 61-71. (pocket guidance available online at: www.uroweb.org/guidelines/online-guidelines/. Accessed 30 November 2012

13. Schroder F et al, Screening and prostate-cancer mortality in a randomised European study. NEJM 2009; 360: 1320-0

14. Schroder F et al, Prostate-cancer mortality at 11 years of follow-up. NEJM 2012; 366: 981-90

15. Heijnsdilk E et al, Quality of life effects with prostate-specific antigen screening. NEJM 2012; 367: 596-605

16. Andriole g et al, Mortality results from a randomised prostate-cancer screening trial. NEJM 2009; 360: 1310-9

17. Horwich A et al, Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21 (suppl 5): v129-v133

18. Ploussard G et al. The prostate cancer gene 3 (PCA3) urine test in men with previous negative biopsies: does free-to-total prostate-specific antigen ratio influence the performance of the PCA3 score in predicting positive biopsies? BJU Int 2012; 106: 1143-7

19. Remzi M et al, follow-up of men with an elevated PCA3 score and a negative biopsy: does an elevated PCA3 score indeed predict the presence of prostate cancer? BJU Int 2012; 106: 1138-41

20. Prostate cancer: diagnosis and treatment: quick reference guide. National Institute for Health and Clinical Excellence, February 2008. Available online at: http://guidance.nice.org.uk/CG58. Accessed 19th November 2012

21. Prostate cancer: a guide for patients. Patient information based on ESMO clinical practice guidelines. Available online at: http://www.esmo.org/fileadmin/media/pdf/2012/patients/summaries/en/Prostate_Cancer_Guide_for_Patients_RCT_ESMO_2012.1.pdf. Accessed 7th November 2012

22. Prostate cancer: diagnosis and treatment. Clinical Guideline 58. National Institute for Health and Clinical Excellence, February 2008. Available online at: http://guidance.nice.org.uk/CG58 Accessed 19th November 2012

23. NCRI cancer trends factsheet for prostate cancer. Available at www.ncri.ie. Accessed 19th November 2012

24. Bill-Axelson A et al, Radical prostatectomy versus watchful waiting in early prostate cancer. NEJM 2011; 364: 1708-17

25. Wilt T et al, Radical prostatectomy versus observation for localized prostate cancer. NEJM 2012; 367: 203-13

26. Walsh P et al, Localized prostate cancer. NEJM 2007;357:2696-705

27. Kohli M and Tindall D, New developments in the medical management of prostate cancer. Mayo Clin Proc. 2010; 85: 77-86

28. Chuu C-P et al, Androgens as therapy for androgen receptor-positive castration-resistant prostate cancer. J Biomedical Science 2011; 18: 63-74

29. Suprefact® Available online at www.medicines.ie. Accessed 19th November 2012

30. Zoladex® Available online at www.medicines.ie. Accessed 19th November 2012

31. Vantas 50 implant® Available online at www.medicines.ie. Accessed 19th November 2012

32. Decapeptyl 3-month® Available online at www.medicines.ie. Accessed 19th November 2012

33. Prostap SR®. Available online at www.medicines.ie. Accessed 19th November 2012

34. Casodex® Available online at www.medicines.ie. Accessed 19th November 2012

35. Drogenil® Available online at www.medicines.ie. Accessed 19th November 2012

36. European Public Assessment Report (EPAR) for Firmagon®. Available at www.ema.europa.eu (Doc Ref: EMEA/CHMP/63576/2008). Accessed 19thNovember 2012

37. Androcur® Available online at www.medicines.ie. Accessed 30th November 2012

38. Crook J et al, intermittent androgen suppression for rising PSA level after radiotherapy. NEJM 2012; 367: 895-903

39. Taxotere® Available online at www.medicines.ie. Accessed 19th November 2012

40. Zytiga® Available online at www.medicines.ie. Accessed 19th November 2012

41. (EPAR) European Public Assessment Report for Zytiga®. Available at www.ema.europa.eu (Doc Ref: EMA/CHMP/542871/2011). Accessed 19thNovember 2012

42. Zytiga approved by NCCP for use in patients who have progressive metastatic prostate cancer following chemotherapy from 1st December 2012. [Personal communication]

43. Jevtana® Available online at www.medicines.ie. Accessed 19th November 2012

44. Antonarakis Es and Armstrong AJ, Evolving standards in the treatment of Docetaxel-refractory castration-resistance prostate cancer. Prostate Cancer prostatic Dis. 2011; 14: 192-205

45. Sturge, J. et al. Bone metastasis in prostate cancer: emerging therapeutic strategies Nat. Rev. Clin. Oncol. 2011:doi:10.1038/nrclinonc.2011.67

46. National Prostate Cancer GP Referral Form. National Cancer Control programme. Available for download at: http://www.hse.ie/eng/services/Find_a_Service/National_Cancer_Control_Programme/Health_Professional_Information/Prostate_Referral_Form.pdf