PSA I Love You: prostate cancer screening in Ireland

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Abstract

Ireland has the second highest rate of prostate cancer (PCa) in Europe and this is largely due to the increased use of PSA testing in Ireland in recent years. Rapid Access Prostate Cancer Clinics (RAPC) were introduced in 2009, in order to increase the organisation and efficiency of PCa diagnosis in Ireland.

The use of PSA as a screening tool is controversial. At present, there is no evidence for the introduction of widespread, population-based screening for PCa. Two large randomised studies which evaluated the efficacy of PSA testing are examined in this review. These are the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) and The European Randomised Study for Prostate Cancer (ERSPC). These studies demonstrated conflicting results. The PLCO reported that there was no evidence that PSA screening reduced PCa-related mortality, while the ERSPC showed PSA screening was associated with a 21% decrease in PCa related mortality.

Following the publication of these trials, the European Association of Urology and the American Urology Association produced new PCa screening guidelines. These guidelines advised against widespread screening programmes but recommended PSA testing in men who met certain criteria (based on age, life-expectancy and other risk factors). In Ireland, there are currently very little national guidelines in relation to PCa screening. However, much opportunistic testing occurs and patients often request PSA tests in a GP setting. National guidelines for PSA screening, which are in line with the AUA (American Urology Association) and EAU (European Association of Urology) guidelines, need to be introduced in order to prevent overtreatment and over-diagnosis of asymptomatic prostate cancer.

Introduction

Prostate cancer (PCa) is the second most common cancer in males worldwide after lung cancer, with over 1.1 million cases diagnosed in 2012[1]. In Ireland today, PCa is the most prevalent non-skin cancer and the second most frequent cause of cancer mortality in men[2]. At present, it has an incidence rate of 156.4/100,000 in Ireland[2]. The majority of cases (97%) are diagnosed in patients older than 50 years[3].

The prostate is a small gland in the male reproductive system that helps to produce and store semen. It is divided into four anatomically distinct zones with the majority of cancers (70%) developing in the peripheral zone[4]. In most cases, PCa progress very slowly but there are rare aggressive forms. Most early stage cancers are asymptomatic but some can present with pain, urinary difficulties and sexual dysfunction[5]. The five-year survival for prostate cancer is very high (93.4%) and the majority of men die with the disease rather than from it[3].

According to the European Association of Urology (EAU) digital rectal exams[6], serum concentration of prostate specific antigen (PSA) and transrectal ultrasound (TRUS) are the main diagnostic tools for PCa[7]. Abnormal findings on a DRE or a raised serum PSA concentration may indicate PCa but a firm diagnosis depends on histological examination using TRUS. The exact cutoff for PSA serum concentration has yet to be defined but a threshold of >4ng/ml is commonly used in clinical practice[7]. The most prominent grading system used for prostate cancer is the Gleason grading system[8]. The Gleason grade is based

on the histological patterns of the tumour, using a 5-point scale. A Gleason score of 6 or less indicates a low-grade tumour, a Gleason score of 7 represents an intermediate grade tumour and Gleason scores 8-10 indicate high-grade tumours. The Gleason system is the most dominant prognostic factor in PCa today and is a powerful tool used to determine treatment choice. Prostate cancer treatment is largely dependent on the stage of the disease (see table 1). The EAU recommends active surveillance, radical prostatectomy (RP), radiation therapy (RT) and transperineal brachytherapy for clinically localized disease. Hormonal therapy (Lutenising hormone-releasing hormone (LHRH) agonists, gonadotrophin releasing hormone (GnRH) antagonists and androgen deprivation therapy (ADT)) is recommended for advanced disease. Patients who have a relapse following localized therapies should be treated with salvage RT, ADT, LHRH agonists or salvage RP. In patients with castration-resistant prostate cancer, ADT should be stopped and they may be started on docetaxel, abiraterone acetate or enzalutamide[9].

CLINICAL POINTS

In Ireland today, prostate cancer is the most prevalent non-skin cancer and the second most frequent cause of cancer mortality in men. At present, it has an incidence rate of 156.4/100,000 population

The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) and The European Randomised Study for Prostate Cancer (ERSPC) are two large randomised trials evaluating the efficacy of PSA screening

The PLCO reported that there was no evidence that PSA screening reduced PCa related mortality

The ERSPC showed PSA screening was associated with a 21% decrease in PCa related mortality

Following the publication of these trials, the European Association of Urology and the American Urology Association produced new PCa screening guidelines

PSA is a serine protease released solely by the prostate epithelial cells[10]. PSA serum levels rise in PCa but notably PSA also rises in a number of other pathologies such as benign prostatic hypertrophy, infection or chronic inflammation[11]. PSA is therefore prostate specific but not prostate cancer specific.

Prostate cancer incidence in Ireland

Ireland has the 4th highest rate of prostate cancer in Europe, 50% higher than the EU average[3]. However, Ireland's cancer mortality rates rank 12th in Europe, only 12% higher than the EU average[3]. Mortality: incidence ratios are second lowest in the EU, with only one death for every 10 men diagnosed[3]. The high rate of prostate cancer in Ireland has arisen due to the increased amount of PSA screening in recent years. The use of PSA screening increased by 19-fold between 1994 and 2005 in Ireland[13].

The rates of prostate cancer in Ireland have increased dramatically over the last 15 years. Currently, 3,267 new cases are diagnosed every year in Ireland, making it Ireland's most prevalent cancer[2]. The majority of deaths (70.3%) from prostate cancer occur in those aged above 75 years, at a median age of 80 (figure 1)[2]. According to data from the National Cancer Registry, Irish men have an

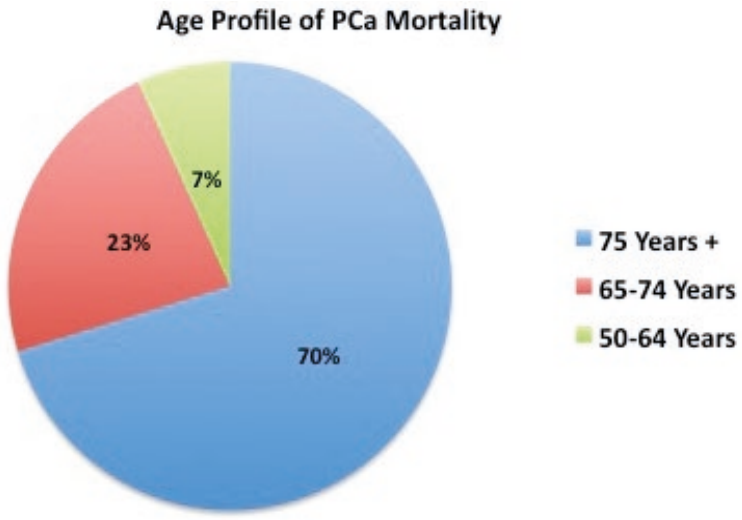

figure 1 The age profile of PCa-related deaths in Ireland[4]

table 1 EAU recommendation for treatment of prostate cancer[11]

Early stage disease	Advanced stage	Relapsed disease following localised treatment	Castration-resistant prostate cancer
Active surveillance	LHRH agonists • Goserelin • Leuprorelin • Buserelin • Triptorelin	Salvage radiation therapy	Stop ADT
Radical prostatectomy	GnRH • Degarelix	ADT • Bicalutamide • Flutamide • Cyproterone acetate	Docetaxel
Radiation therapy	ADT • Bicalutamide • Flutamide • Cyproterone acetate	LHRH agonists • Goserelin • Leuprorelin • Buserelin • Triptorelin	Abiraterone acetate
Transperineal brachytherapy		Salvage radical prostatectomy	Enzalutamide

11.9% cumulative lifetime risk of developing prostate cancer, but only a 1.1% risk of mortality from their disease[14]. The five-year survival rate for prostate cancer has risen from 68.8% in 1997 to 93.4% in 2009 (figure 2)[2].

Risk associated with PSA screening

Potential harms of the detection process

It is thought that approximately 42% of prostate cancers diagnosed by PSA screening would not have caused any clinical problems within the patient's lifetime meaning the patient would have died with the disease rather than from it[13]. This opens up the argument that perhaps widespread PSA screening could pose a significant health risk rather than act as a useful screening tool. Specifically, the PSA test itself causes mild complications (dizziness, fainting, bleeding and hematoma) occurring at a rate of 26.2 per 10,000[15]. Moreover, a significant number of false positives occur in PSA screening. When thresholds between 2.5 and 4.0 µg/L are employed, approximately 80% of positive results are found to be false positives[14]. Most false positives can be attributed to benign prostatic hyperplasia, ejaculation, prostatitis, perineal trauma, cystitis or recent use of instruments in the urinary tract[13]. Men who receive a false positive result may suffer from negative psychological effects such as anxiety about prostate cancer diagnosis. In addition, roughly one third of men who undergo a biopsy following a positive PSA result will suffer from pain, fever, haemorrhage, infection and transient urinary problems[14]. Undergoing a biopsy can be stressful for men and some may experience persistent anxiety even following a negative biopsy result[13].

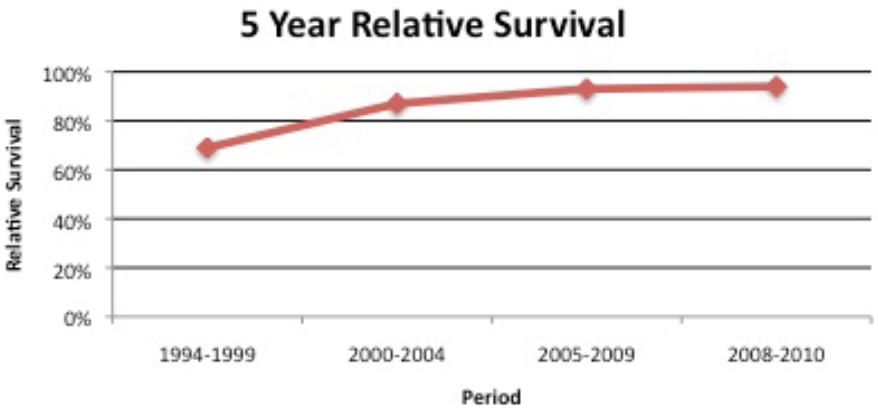

figure 1 the five-year survival rate since 1994[4]

Risks associated with earlier onset treatment

The main treatments for prostate cancer in Ireland are active surveillance, radical prostatectomy, external beam radiation therapy, brachytherapy, hormone therapy and chemotherapy[9]. Radiotherapy and surgery can result in some serious adverse effects; erectile dysfunction and urinary incontinence occurs in at least 20-30% of men treated with these therapies[14]. Androgen deprivation therapy, although not FDA approved, has been used as first-line therapy for early-stage PCa and is associated with hot flushes, erectile dysfunction, gynaecomastia, anaemia, osteoporosis, depression and fatigue[14]. According to the USPSTF, of the men that undergo PSA screening, a higher proportion will experience adverse events from the diagnostic tests or treatment, than will benefit from the screening.

International studies on PSA screening

Two large randomised trials, carried out in America and Europe, examining the efficacy of PSA screening, have been published. These are The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial[15] in the U.S. and The European Randomised Study of Screening for Prostate Cancer[16] in Europe. While both articles, were printed in the same issue of The New England Journal of Medicine in March 2009, both showed conflicting results!

The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

The PLCO was carried out between 1993 and 2001, in 10 different study centres across North America. Men (n = 76,693), aged between 55 and 74 years, were randomly assigned to either the standard care (control) group or the screening group (PSA & DRE annually for 4 years). At 7 years, more cases of prostate cancer were diagnosed in the screened group (2,820) than the control group (2,322), a relative increase of 22%[15]. At 10 years, there were 92 deaths in the screening group compared to 82 in the control group[15]. Therefore in comparison to the control group there was no reduction in PCa-related mortality in the screened group.

However, there are some important factors that may have played a part in lack of reduction in PCa mortality in the screening group. In the ERSPC a threshold of 3ng/ml was used. This increased the sensitivity of this test and allowed the diagnosis of more prostate cancers. By contrast, a PSA threshold of 4ng/ml was used in the PLCO trial. Secondly, 'PSA contamination' (a subject in the control group undergoing PSA screening) was carried out by 56% of control subjects by the end of the trial. This substantial number may have diluted down the results of the screening group. Another factor was that 44% of subjects in both groups had already undergone a PSA test at baseline. Fourthly, PCa therapy improved over the course of the trial, reducing the number of deaths in both groups. Lastly, the effect of PSA screening on PCa-related mortality may take many years to show a benefit so further evaluation on these trial subjects must be done at 15 years[15].

The European Randomised Study of Screening for Prostate Cancer

The ERSPC screening trial, randomly assigned 162,243 men aged between 55 and 69 years to either the control (receiving standard care) or screening group (receiving PSA screening every four years, on average). The trial was carried out in eight European countries and results evaluated at a median follow-up time of 9 years[16].Subsequent analysis of the data was at a median follow-up time of 11 years[17]. Prostate cancer incidence in the screened cohort was much greater than the control cohort (8.2% vs. 4.8%)[16]. The absolute risk difference was 0.71 deaths per 1000[16].Using this data, it was concluded that 1,410 males would require screening and 48 would need to be diagnosed in order to prevent one PCa death[16]. At 11 years, there was a relative reduction in PCa mortality of 21% in the screening group. In

order to prevent one PCa death, 1,055 men would require screening and 37 cancers would need to be diagnosed[17]. These improved figures in the subsequent analysis are in line with the view that the benefit of PSA screening increases with longer follow up time. The ERSPC concluded that PSA-based screening significantly decreases PCa-related mortality but is associated with a large amount of over-diagnosis[17].

International prostate cancer screening guidelines

The U.S. Preventative Services Task Force

Following the results of the PLCO and the ERSPC the U.S. Preventive Services Task Force (USPSTF) published a recommendation opposed to PSA screening, (table 5)[17]. The reason for this recommendation was due to the harms associated with PSA screening (overtreatment, bowel and erectile dysfunction and urinary incontinence) relative to its benefits (PCa- related deaths averted). Although the USPSTF discourages PSA screening it does acknowledge that some patients will request it. The USPSTF therefore recommends that any patient undergoing screening should be fully informed of the risks, as well as benefits, prior to testing.

The American Urological Association guidelines

The American Urological Association recently published new guidelines for the early diagnosis of PCa using PSA testing (table 2)[20]. These new guidelines are as follows:

1. PSA screening is not recommended in men <40 years
2. PSA screening is not recommended in men between 40-54 years with average risk
3. Shared decision making for PSA screening is recommended in men aged 55-69 years
4. The screening interval should be ≥2 years
5. PSA screening is not recommended in men >70 years or in men with a life expectancy of ≤10-15 years.

The European Association of Urology guidelines

The European Association of Urology guidelines differ from those of the AUA (table 5)[7]. The current EAU guidelines state that there is no evidence for the introduction of widespread population-based screening programmes for early diagnosis of PCa[21].

The patient and his physician should make a shared decision whether to undergo PSA testing for the early detection of PCa. A baseline PSA level should be obtained at 40-45 years of age and a subsequent screening interval should be determined from this level. Men aged 45-59 with an initial level of ≥1.0ng/ml should be tested every 2-4 years whereas men with a level of ≤1.0ng/ml need only to be screened every 8 years[7]. Men aged more than 75 years, with a level of ≤3ng/ml, do not require further PSA testing[21]. A significantly increased risk of PCa-related mortality and diagnosis of advanced disease is associated with patients that have a baseline serum PSA level ≥1ng/ml at 45 years or a baseline serum PSA level ≥2.0ng/ml at 60 years[7]. Using these levels, it is possible to target the high-risk group; this will avoid over diagnosis and reduce costs associated with frequent screening in the low risk group.

Guidelines in Ireland

There are currently very few guidelines in place in Ireland in relation to prostate cancer screening. Neither the HSE nor The Irish Cancer Society recommends widespread population based screening in Ireland. At present in Ireland, many men undergo optional PSA testing in a primary care setting. There is much variation in practice, most likely due to the absence of national guidelines. The HSE recommends that no patients undergo PSA screening without being fully informed on the implications of a positive result.

There is a need for more definite national prostate cancer screening guidelines that are in line with

those in other countries. The HSE needs to adopt a set of guidelines based on the EAU or AUA guidelines outlined above. National PSA screening is not recommended in any country but protocols must be put in place for those men who opt for PSA screening.

Drummond and colleagues showed that although PSA testing is used considerably throughout Ireland, it is not being used efficiently[13]. A significant percentage of PSA testing occurs in males aged <50 and >70 years and men with very low baseline levels (<1.0ng/ml), undergoing frequent repeat tests[19]. These findings suggest that many men in Ireland are undergoing nonessential PSA testing that is not cost effective and leads to over-diagnosis. Both the EAU and the AUA advise against testing men <40 years and those with a life expectancy of <10 years. Ireland must follow other European countries and form guidelines for PSA screening in order to prevent the unnecessary testing of men in these low risk groups.

Conclusion

Prostate cancer detection in Ireland has risen considerably in recent years due to increased use of PSA testing. There are still uncertainties as to whether the advantages of PCa screening using PSA outweigh the risks. Although there is no organisation in Ireland that recommends widespread population based screening, many men still undergo PSA testing in a primary care setting. Ireland urgently needs guidelines for PSA screening based on current evidence from the most recent literature. The guidelines should emphasise the importance of shared decision-making between patient and their physician prior to undergoing PSA screening. The guidelines should also outline the optimal PSA threshold for biopsy, the age groups and high-risk groups eligible for screening, the screening interval and the criteria for discontinuing screening. These guidelines are necessary to ensure that clinically significant prostate cancers are caught in an early treatable stage and also to minimise the amount of over-diagnosis and over treatment of asymptomatic tumours.

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