CONTROVERSIAL TOPICS IN SURGERY
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Screening for prostate cancer

We shall follow this topic in the May issue of the Annals with two articles discussing radical prostatectomy..

Now that men realise that they have a high chance of developing prostate cancer it is unsurprising that they are keen to detect it as early as possible. Whilst screening by means of PSA and digital rectal examination has become the norm in the US and is widely practised in mainland Europe, it has never been official health department policy in the UK. The reasons for this difference in practice are well-illustrated by the articles by Donovan et al. and Malone. There is little doubt that screening will detect a significant number of tumours but not all of these are necessarily clinically-relevant. The presence of false-positives and some false-negatives, the morbidity of the screening process and its cost all raise serious questions about its true worth. It will take some years before the trials currently in progress can begin to answer these questions.

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The case for

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With the exception of the much criticised[1] Quebec study,[2] reports are still awaited from randomised trials comparing populations screened by serum prostate-specific antigen (PSA) against controls. The European study, which is likely to be the first to give any results, is expected to report in 2008[1] so, at present, the debate is limited to analysis of the evidence currently available.

In so doing, the first fact to confront is that the results of treatment have not improved for patients with bony metastases from prostate cancer since Huggins' Nobel prize winning work on androgen deprivation in the 1940s.3

The second, however, is that this is not true for less advanced stages of prostate cancer. In the MRC sponsored study of immediate versus delayed treatment for patients with metastatic and locally advanced prostate cancer,[4] patients with locally invasive cancers and those with lymph node metastases but with a negative bone scan had a significant increase in life expectancy when given hormone treatment before symptoms developed. Even patients with a positive bone scan, treated prior to the development of symptoms, had fewer serious complications (*e.g.* paraplegia) than patients who waited for treatment until they became symptomatic.

The need to administer timely hormone treatment for locally advanced cancers has also been shown in several studies on patients undergoing radiotherapy. Trials sponsored by the EORTC in Europe, and the RTOG in America have shown a statistically significant improvement in survival when patients with extracapsular disease or poorly differentiated localised disease were given adjuvant hormone treatment with their radiotherapy.[5]

Patients with a PSA below 20 ng/ml will, with only rare exceptions, have a negative bone scan;[6] so when patients who present with bony metastases ask if their cancers could have been detected earlier and might they have lived longer as a result of early detection, the answer to both questions is undeniably yes. It would seem reasonable, therefore, to offer patients the chance to have their cancers diagnosed before they reach the stage where treatment will make no difference to their life expectancy. When one considers the growth and development of prostatic malignancy there is no real alternative to screening and in reality this is already happening by another name.

Prostate cancer is a silent cancer. The majority of prostate cancers develop in the periphery of the gland away from the urethra so early local symptoms are not produced.[7] This is why, as late as the decade between 1977 and 1987, in the UK 45% of patients presented with metastatic disease.[8] With the advent of PSA, without any formal screening programmes in the UK, there has been a significant reduction in the number of patients presenting with metastatic disease. The reason is that doctors are increasingly checking the PSA if men have lower urinary tract symptoms or pelvic/bony pain. It is highly likely that in most symptomatic men diagnosed with localised prostate cancer, the symptoms that led to the discovery of their cancers were from benign prostatic hypertrophy, the pelvic pain syndrome or arthritis. Although by strict criteria this is not screening, in reality it is a first cousin. It might be just as valid to tell people to have a PSA test if they develop heartburn or angina and more honest to admit to the population that there is very little correlation between symptoms and the presence of cancer.[9]

One reason to screen, therefore, is to bring order to the chaos whereby the country's medical services are being geared to the treatment of cancers detected by the presence of symptoms, which, in many cases, are irrelevant to the presence of prostate cancer. It is illogical and if one stands back it is almost farcical. In addition, because early symptoms of prostate cancer are so infrequent, many patients still present with metastatic disease.

The case for radical treatment of organ confined cancers remains more controversial. Holmberg *et al*.[10] recently reported the only randomised control trial of radical prostatectomy versus watchful waiting. They showed that there was a significantly reduced rate of local progression, development of distant metastases and death from prostate cancer in the radical prostatectomy group but the overall mortality was not (yet) statistically improved. Moreover, in the Austrian province of Tyrol, where PSA testing has been made freely available from 1993 with wide acceptance by men in the population, there has been a significant reduction in prostate cancer mortality compared to the rest of Austria. It may be argued that this is due to effective radical treatment for early cancers or the timely use of hormones in more advanced cases and on the current evidence no one can be certain. This does not mean, however, that the case for screening evaporates, far from it as either way screening has given a survival advantage.

The level of PSA for most screening studies is generally set around 3–4 ng/ml on the basis that most cancers detected at this level will be organ confined and amenable to radical surgery or radiotherapy. It seems certain, however, that a PSA cut-off at this level will detect more cancers than are likely to present clinically. In an elderly population, many men may die with their cancers rather than because of them. It is possible to be more selective in the screening process either by setting the level of PSA higher or by looking at the rate of rise and a trial of screening with a cut-off of PSA 3 versus 10 or 15 might be much more telling than the current trials being undertaken.

Urologists appear to be cornered into a situation where only two possibilities are being considered, namely to detect all cancers at an early stage or to do nothing. As screening is the only reliable way of detecting prostate cancer before bony metastases become evident, the real question is not whether to screen but what level of PSA should trigger biopsy.

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The case against

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Across the world, the suitability of prostate cancer for population screening continues to be highly controversial, fuelled by advocacy in the absence of robust evidence.[1] The aim of screening for prostate cancer would be to find potentially life-threatening tumours efficiently and safely among asymptomatic men, at a stage when lesions could be cured by effective treatment, leading to improvements in the quantity and quality of men's lives. As screening requires intervention in healthy populations, the balance of evidence should convince that the prospect of benefit outweighs harm.

There is no doubt that prostate cancer is a serious problem. It is rapidly becoming the most common cancer in men, with over 500,000 new cases estimated across the world in 2000, and it is a major cause of death in older men, second only to lung cancer among cancer deaths. Autopsy/post mortem studies have shown that prostate cancer is very common, with very many small tumours found in men dying of other causes. The life-time risk of having microscopic evidence of prostate cancer for a man of 50 years is 42%, while his risk of dying of it is only about 3%.[2]

Identifying potentially treatable tumours

Serum prostate-specific antigen (PSA) testing followed by transrectal ultrasound-guided needle biopsy allows the detection of prostate cancer in some men who might benefit from radical intervention (between 50 and 70 years of age). Prostate cancer can be found in between 2%[3] and 40%,[4] depending on the intensity of the screening effort – such as the number of PSA tests, level of PSA cut-point, number and frequency of biopsies undertaken. PSA is not prostate cancer-specific and can be raised in other circumstances, leading to a large number of false-positives (cancer is not found in around 70% of men with raised PSA levels who undergo biopsy). The simple PSA blood test is safe and acceptable, but biopsy can be uncomfortable or painful and carries risks of bleeding and infection. In addition, there will be an unpredictable number of false-negatives who later develop prostate cancer in the presence of a 'normal' PSA test: 36.5% of detectable tumours were identified in the majority of men who had PSA levels below 4 ng/ml in the European Randomised Screening Trial (ERSPC).[5]

Even amongst those diagnosed with localised prostate cancer, there are further uncertainties. Likelihood and speed of tumour progression is currently impossible to predict. Tumours with high Gleason grades are more likely to progress, but the risk of death within 15 years of diagnosis ranges from 60–80% for those with the highest scores (8–10) to 4–7% with scores of 2–4, and 18–30% for the most common screen-detected score of 6.[6]

Current screening techniques, therefore, enable tumours to be detected with the potential for cure; however, as it is currently impossible to distinguish between indolent and life-threatening lesions, there is potential for considerable over-treatment of insignificant disease.

Treating localised prostate cancer

Treating people when it is unclear whether or not they will benefit becomes a particularly serious issue when the treatment itself produces harm. Treatments for localised prostate cancer include radical prostatectomy, radical radiotherapy, brachytherapy, hormone manipulation, or programmes of monitoring, variably termed 'watchful waiting', 'surveillance' or 'active monitoring'. Published evidence about the effectiveness of these treatments is limited by their tendency to be observational in design, small in scale and insufficiently robust. A trial from Scandinavia showed that prostatectomy reduced the risk of death from prostate cancer at 8 years by approximately half compared with watchful waiting (relative hazard 0.5; 95% CI 0.25–0.84).[7] However, this study has little relevance for screening as only 5% of these men had screen detected prostate cancer.

Each of the treatments for localised prostate cancer can have deleterious side effects, reported at various levels depending on patient selection, specialist skill and throughput.[8] Radical prostatectomy, for example, while having a high cure rate, can lead to 2–5% of men having severe incontinence, up to a half experiencing some leakage of urine, and between 10–90% experiencing erectile difficulties.[9] Evidence from randomised trials about the effectiveness and side-effects of treatment for screen-detected disease is urgently required, but it will be some years before the US PIVOT[10] and UK ProtecT[3] trials report.

Effectiveness of screening programmes

Randomised trials of screening are underway in Europe (ERSPC) and the US (PLCO), and UK data will be provided by a comparison arm alongside the ProtecT trial. Several observational studies of screening have been published, but provide conflicting evidence. In the US, changes in the incidence and mortality of prostate cancer have been attributed to screening,[11] but similar patterns have been recorded in the UK[12] and The Netherlands[13] over the same period in the absence of screening. Perhaps the most compelling evidence comes from a study comparing Seattle-Puget Sound (where there was rapid uptake of PSA screening and prostate cancer treatment) and Connecticut (where testing was much less common).[14] Men in Seattle-Puget Sound were 5.39 times more likely to undergo PSA testing, 2.2 times more likely to undergo biopsy, and there were 5.9- and 2.3-fold higher rates of radical prostatectomy and radiotherapy than in Connecticut. However, no differences in mortality were found, even with 11 years of follow-up.[14] Such observational evidence has to be interpreted with caution, but evidence of a mortality benefit from screening is still awaited.

Conclusions

If screening for prostate cancer were introduced today, men aged between 50 and 70 years would face an uncomfortable burden of uncertainty and harm. For every 1 million men who agreed to the simple PSA blood test, about 100,000 would have a raised (abnormal) PSA result and face anxiety over possible cancer and the need for biopsy, leading to further anxiety, discomfort and (rare) risk of sepsis. Approximately 20,000 men would then be diagnosed with cancer, and 80,000 would face the anxiety of uncertain future risk. If one half of those diagnosed with localised disease (10,000) underwent radical prostatectomy, about 10 would die of the operation and, even in the best hands, around 300 would develop severe urinary incontinence and 4000 erectile dysfunction. The number whose prostate cancer would eventually have impinged upon their lives is currently unknown, as is the number of deaths that would be have been prevented. On-going randomised trials will provide evidence about current screening programmes. Key issues for further research are to determine the genes, pathways or molecular changes that drive the aggressiveness of prostate cancer and predict which cancers will progress to threaten lives.

Today, the likelihood of harm outweighs the prospect of benefit, leading to the inescapable conclusion that screening for prostate cancer is unjustified outside randomised trials investigating its effects.

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