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# Editorial

# Do We Know What's Best For Prostate Cancer?

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THERE IS no apparent consensus for the management of prostate cancer and this disagreement is the only common ground amongst clinicians. Medical opinion is divided over the treatment of both small bulk local disease and advanced tumours, but is this lack of agreement reasonable, or is there sufficient evidence-based trial work available to provide treatment guidelines?

The extraordinary increase in death rates in prostate cancer has led to the instigation of screening programmes, and these are driven by the philosophy that early detection will lead to a reduction in death rates. But is screening effective and does treatment prolong life? The effectiveness of screening programmes depends upon the willingness of apparently well men to come forward to be examined and have blood tests, and hinges upon the accuracy of those examinations and blood tests. Well men, unlike well women, are extraordinarily unwilling to attend for medical examinations. The reasons for this are unclear and cut across sociological and psychological phenomena. However, the reluctance of men to have screening tests for prostate cancer could be considered entirely rational because screening tests for prostate cancer so lack specificity. The rectal examination is notoriously subjective and prostate specific antigen (PSA) ought to be more aptly termed "prostate non-specific antigen" because it is elevated in benign enlargement of the prostate and many other conditions such as prostatitis and even breast cancer. PSA lacks specificity as a screening tool, and in the Physicians Health Study was evaluated in only 47% of men who went on to develop prostate cancer 4 years from enrolling in the study [1]. Diagnostic specificity can be increased to 75% by a combination of PSA, rectal examination and rectal ultrasound [2].

There is vociferous controversy concerning the management of early stage prostate cancer diagnosed in screening programmes. Management options include observation, radical radiation or radical surgery. Progression rates depend upon grade and stage, and range between 10–85% over 10 years, whichever management option is pursued [3]. Active treatment should, therefore, be considered inappropriate for the asymptomatic elderly patient with a well or moderately differentiated T1 or T2 tumour, which is associated with a progression rate of less than 10% over 10 years [4]. Many surgeons argue that younger men with poorly differentiated tumours should be treated by radical surgery, but this is irrational because, except in highly selected series, only 10–15% of these patients survive 10 years [5]. Despite claims to the contrary, detailed analyses show that, even with radical nerve sparing procedures, a degree of incontinence is present in 40% of patients and impotence in 70% [6]. When considering alternatives to surgery, it should be remembered that radical radiation to the prostate also has morbidity. Acutely there may be distressing proctitis or cystitis, and long-term side-effects include impotence. The reason why opinions are so divided on the management of early stage prostate cancer is that there have been no randomised trials, involving significant numbers of patients, that have compared survival and progression rates in patients treated with radiation or surgery or managed by observation. As the results of following either option are not excellent and there are side-effects from treatment, the patient with incidental asymptomatic prostate cancer, diagnosed in screening programmes, ought to be managed by "watchful waiting", and treated only when symptomatic.

Large bulk, locally advanced prostate cancer traditionally has been treated by hormonal therapy. This is because radiation therapy is ineffective at sterilising T3 and T4 prostate cancer. Patients with this disease stage have a reasonable median survival, reasonable, that is, in the context of a median age of presentation of 72 years. For the younger patient, the prospects of 4.5 years median survival is far from heartening. Attempts have been made to improve upon the prospects for survival in this group of patients by hormonal down-staging prior to radical radiotherapy or prostatectomy. Anti-androgen therapy usually is given for a period of 3 months prior to the institution of local radiotherapy or radical surgery. The majority of patients have a local response with a 35% reduction of the prostatic mass [7]. This allows a 30% reduction in rectal dosing [8]. However, this approach is ineffective in reducing local recurrence rates and limiting distant progression. In the context of surgical down-staging, 40% of patients remain with metastatic disease in lymph nodes at the time of operation [7]. In summary, there is no role for primary hormonal therapy in the down-staging of prostatic tumours prior to radical radiation or surgery.

Currently, locally advanced or metastatic prostate cancer is treated by androgen deprivation. The gonadotrophin releasing hormone agonists were introduced into the treatment of prostate cancer in the 1980s. These compounds limit testicular

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androgen production and may also have a direct effect on the tumour [9]. It was argued most publicly, that in a disease that is androgen-sensitive, it is important to remove all sources of androgen production. In addition to the testes, significant amounts of androgen are produced by the adrenals and absorbed from dietary sources. Treatment with a leutenising hormone releasing hormone (LHRH) agonist or by castration reduces testicular sources of androgen. The addition of an agent blocking the binding of androgen to androgen receptors limits the effects of adrenal and dietary androgens.

This hypothesis was greeted initially with an enormous amount of scepticism but, such was the interest that surrounded the concept, that a number of clinical trials were instigated to investigate the hypothesis. The first to be published was run by the National Cancer Institute (NCI) and involved 603 patients with metastatic disease [10]. A 7-month survival advantage was found for combination therapy as compared with single agent LHRH agonist treatment. The second important study to publish survival data was from the European Organization for Research and Treatment of Cancer (EORTC) [11]. This randomised 300 patients to LHRH agonist therapy and anti-androgen or to orchiectomy. The findings of this study were identical to those of the NCI trial; a 7-month survival advantage was found for patients treated with combination hormonal therapy.

Despite these emphatic results, there is fervid debate over the advantages of combination therapy. Recently, a meta-analysis has been undertaken to resolve the issue of maximal androgen blockade [12]. Twenty-five trials were examined and data were available for analysis in twenty-three. However, this meta-analysis was flawed because dissimilar treatments were compared. In these trials, three different anti-androgens were used in a total of seven different dosage regimens. Like was not compared with like as each anti-androgen acts entirely differently. Cyproterone acetate is an androgenic progestogenic agent that inhibits testicular and adrenal hydroxylase action, displacing testosterone from its binding proteins and limiting the interaction of the testosterone binding protein complex with DNA. Nilutamide is an adrenal hydroxylase inhibitor, whilst flutamide acts at the level of the androgen receptor, competing with testosterone and dihydrotestosterone for binding sites. The authors concluded that there was no overall benefit from these agents. However, this meta-analysis is fatally flawed as only two of the studies examined presented survival data and both of these showed a significant benefit to combination therapy. In addition, combination therapy provides the twin advantages of preventing tumour flare, and allowing the patient the chance to respond to flutamide withdrawal.

How should we treat patients with recurrent prostatic cancer? Chemotherapy is not helpful, but radiation therapy offers effective pain palliation. Thirty to forty per cent of patients treated by flutamide or casodex withdrawal respond [13, 14]. This high response rate, which is without toxicity, makes anti-androgen withdrawal a prime therapeutic manoeuvre. There has been interest in suramin treatment. This agent, which inhibits growth factor activity, contrasts in the complexity of its administration and myriad side-effects with anti-androgen withdrawal, but may have some value because of the recently reported possibility of fixed-dosage scheduling, and the long duration of responses [15]. We remain uncertain whether suramin is an active agent, as patients are concurrently treated with hydrocortisone to limit its toxicity, and steroids are themselves active second-line treatments for relapsed prostate cancer [16].

So, do we know what is best for prostate cancer? Evidence-based data clearly show patients and their clinicians the current best buy treatments in the prostate cancer medical hypermarket. For small bulk disease, it has yet to be proven that there is an advantage to any active therapy as compared with a watchful waiting policy, and so observation is the management policy of first choice. Screening as it currently stands has no useful role in the early detection of tumours. There is no advantage to neo-adjuvant therapy in the management of large, bulk, locally advanced prostate cancer. The best treatment for symptomatic locally advanced disease or metastatic cancer is a combination of an LHRH agonist with flutamide and for relapsed disease, anti-androgen withdrawal.


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