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What are we Aiming to Achieve in Our Patients with Advanced Prostate Cancer

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Abstract

Advanced Prostate cancer covers a wide spectrum, ranging from a rise in PSA to the presence of multiple metastases. It remains a truism that hormone naïve patients respond to hormones and in many second and third line responses do occur. Most men with the disease have competing morbidities and as accurate a prognosis overall is essential for patients at whatever stage their advanced cancer has reached. Deferring therapy, on the current evidence is the default position but regimes need to be tailored to ensure that each patient achieves their maximum quality of Life.

Keywords: Advanced prostate cancer; Hormones; Chemotherapy; Novel therapies; Rising PSA; Quality of life

Editorial

Advanced Prostate Cancer is a Humpty-Dumpty word meaning exactly what I say it means neither more nor less [1]. It covers a situation of minimal rise in a PSA level after definitive therapy, but appears to have significantly different prognosis if the prostate has been removed or not, to patients with a heavy burden of metastatic disease. The only common factor is that in hormone naïve patients all respond to androgen deprivation therapy, the duration of which is variable but appears palliative and not curative.

Thirty five years ago when Patrick Walsh carried out his first anatomic radical prostatectomy [2], managing Prostate Cancer was fairly clear and excited little debate. 50% of patients presented with localized disease and were treated with a variety of contrasting therapies, radical surgery, radiotherapy, immediate hormone therapy, and observation, although in low risk, low volume cases in men in their 60s and over, the tendency was to discharge them without follow-up. Walsh was going against the received wisdom of his day, which following Jewett's paper of 1975 [3] showed no survivors from patients who had undergone radical prostatectomy in the presence of a poorly differentiated tumour, or high risk in current parlance. However, the rationale for continuing pursuit of a successful surgical outcome was the belief that a percentage, perhaps all, tumours which started out as low or intermittent risk would go onto dedifferentiate and thus cause death but this would be avoided by timely intervention.

The other 50% presented with metatstases, predominantly in the bones, and frequently symptomatically. Hormone therapy either as orchidectomy or oestrogens, had a Lazarus-like effect, and the patients literally took up their beds and walked. The effect was always palliative, but on average lasted two years, when the patients with common cancers of lung or stomach presenting with metatastases lasted only a few months; by these criteria Prostate Cancer was seen as a good tumour.

In 1994 the FDA approved the use of the PSA test in conjunction with digital rectal examination (DRE). The basis of the normal value of PSA was supplied by the first commercial test in 1986 based on a study of 472 apparently healthy men, which found 99% had PSAs below 4.0 ng/ml [4]. This led to the time of the diagnosis of Prostate cancer in the Western hemisphere going backwards, and gave a lead time bias of at least 10 years, this is exemplified by the recent ProTech Study whose report of their 10 years follow up exemplifies this; in c1700 patients randomized between surgery, radiotherapy, and active monitoring, it was found there were only 17 deaths from Prostate Cancer at 10 years, (8 from the active monitoring group, and 9 from the treated groups), with 6% progression apparently twice as many in the observation group as the treated ones, and a 10% overall mortality from other causes [5].

The first part of the last 20 years proved quite difficult for patients and clinicians alike. Surgery was the principal mode of therapy and many patients post surgery developed a detectable PSA. This, in the absence of evidence, led to their being treated with hormones immediately, which then produced the iatrogenic condition of non-metastatic hormone resistant prostate cancer. Lack of evidence could not determine whether the disease outcome eventually, had possibly been accelerated by early hormone intervention. Radiotherapy also had their hormone moments. Trials at the beginning of the millennium suggested that R/T combined with hormones enabled patients to do better that with R/T alone, and the complimentary study comparing R/T against hormones alone suggested that the added R/T was beneficial [6]. D'Amico in an update of his 2004 paper, in 2015, showed that, long term, there was no survival benefit for the combination, and that there was reduced survival in men with moderate to severe co morbidities [7].

In 2004, Tannock showed that Docetaxal had some effectiveness in apparently hormone resistant prostate cancer, [8] while in 2011, de Bono showed abiraterone and prednisone had activity in these patients, [9] and the following year Scher showed similar benefit with Enzalutamide [10], both the last two agents being super anti-androgens in essence, thus restoring the old belief that prostate cancer remains hormone sensitive long after the first hormone ceases to work. Currently there are up to a score or more adjuvant, neo-adjuvant, and second and third line studies of targeted therapies,

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vaccine based therapies, and trials to bring forward chemotherapy and abiraterone/enzalutamide therapies into earlier stages of the disease when only PSA is rising and the burden of metastatic disease is small. Finally, two significant studies, CHAARTED, and STAMPEDE, have both shown recently an increased survival in patients presenting with metastatic disease when a combination of taxanes and hormones are used compared to hormones alone [11].

From this bewildering array of data what can the prostate cancer patient take from this? First, as 90% are now diagnosed when the disease is localized they will be living with the consequences of the disease and its treatment for many years. From the pitiably few randomized studies of surgical treatment, the theory that tumours left in situ can change their nature would appear to be born out but only to a small degree, possibly 12-15%, so there remains a great deal of potential overtreatment in this group of patients, and therefore, unnecessary complications of treatment [12]. Despite the surgery, up to 40% of patients show a measurable PSA, which the Johns Hopkins study shows takes 8 years to demonstrate metastases and a further 5 years, on hormone treatment, to death [13]. A more recent report shows a 40% metastases free survival rate at 10 years from when the PSA became measurable [14]. These figures are very similar to the EORTC study 30891, which looked at immediate hormone therapy against deferring hormone therapy, in nearly a thousand patients who were randomized; the deferral being until the patient had developed demonstrable metastases in imaging, these in patients who had declined or been unfit for definitive treatment for localized disease. The average was just over 7 years to need to start treatment in the delayed group, and again 5 years on treatment on hormones until death. Half the patients in the deferred arm never needed to start treatment, and although there was a modest overall survival advantage to the immediate group, there was neither Prostate cancer specific mortality advantage nor symptom free advantage as, surprisingly there were less cardio-vascular episodes in the immediate group, and the main clinical concern of catastrophic spinal cord compression, was very uncommon, only 9 cases, shared 4 to 5 between each arm [15].

Starting hormone therapy with the first rise in PSA is almost certainly unnecessary, and on the evidence, expectant treatment would appear to be in the individual patient's long term interests and the default position. How long should therapy be deferred, and what general measures and support are available to patients who may spend many years in this expectant state? Does treatment, in our present state of knowledge offer them anything? Can we define what we are aiming to achieve for our patients?

It is vital that the patient be provided with as much information that they can handle. It must be made very clear to them that they have time to reach a decision, and if they go to the default one of no therapy, they can always change their minds, if they are personally uncertain, and if new information appears. Patients need very positive advice that they have time and they should make the most of it.

All patients should preferably be seen by a physician in order that that a proper assessment of their general health [16], and the prognosis of any other underlying conditions can be presented to them [17]. A strategy for the individual patient needs to be worked out against the worst case background that we are looking at 10 more years, with a further two after initiation of hormones for symptomatic treatment. Some patients, despite the evidence, will desire immediate treatment in the hope, that having gone for cure with definitive treatment that has failed; they would still like to try again. These patients should be encouraged to enroll in new therapy Phase II/III trials for rising PSA without proven metastases, and they are likely to have the motivation to persist with these studies. New therapies could prove effective, and the psychological health of these patients will be preserved. These patients should be discouraged from participating in any but legitimate trials.

Many patients will accept that they have time, and that hormones have side effects they would wish to avoid. In the absence of facts, many would wish to hedge their bets, and are happier to agree arbitrary levels of PSA, or changes in the rate of rise in PSA which can be used as triggers to initiate therapy. It is often better to treat the anxious patient like this in order to improve his quality of life. Various figures have been used, the figure of 20 ng/ml used by the EORTC for intermittent therapy use has the benefit of long usage but different values, 25, 40 may be just as helpful. Intermittent hormone therapy appears equivalent to continuous, and studies do show, even in continuous, conventional hormone therapy, if sequenced with anti-androgens, LHRH, and then oestrogens; a persistent, if diminishing hormone response to second and third line hormones occurs, remembering always that stilboestrol is still a worthwhile agent [18].

If patients can manage psychologically then deferring treatment so that the maximum benefit of current treatment when metastases are present is obtained. However, a continuing dialogue with the patient may enable them to enter trials of new treatments, so keeping available for as long as possible the proven, effective palliative regime.

For a brief period it was hoped that early diagnosis, followed by extirpative therapy would cure all prostate cancers. Now we know this is not so, it is important that our patients are fully aware of the very long duration of this disease and that although the reappearance of PSA, means the disease is probably ineradicable, nevertheless patients have a very long time ahead of them and their continuing management is as much about the avoidance of preventable iatrogenic side effects, as it is about ensuring the maximum possible survival. In this disease, above all cancers probably, patients need the reassurance that nothing happens suddenly, that their general health is the most important element, and that time, for once, is a friend, not a foe.

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