

Topic: How does the prostate cancer microenvironment affect the metastatic process and/or treatment outcome?

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# Getting better at treating prostate cancer: what clinicians should want from scientists

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## ABSTRACT

If the treatment landscape for prostate cancer is to be transformed, clinicians and scientists must work together ever more closely. Prostate cancer defeats physicians when patients are not accurately stratified according to patients' risk of dying of disease, when the effects of tumor heterogeneity are insufficiently understood, and when attempts at therapy by clinicians spur further disease evolution and the emergence of new resistance mechanisms. At the same time, clinicians' over-treat men who in reality do not need it, and some of those men needlessly suffer long term side effects as a result. This commentary is aimed at stimulating debate about how we as clinicians and scientists can assist one another and improve our knowledge to the benefit of patients dying from metastatic disease.

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## WHAT DO CLINICIANS WANT TO KNOW?

"Is cure possible? Is cure necessary? Is cure possible only when it is not necessary?" This - now almost legendary - quote by the late American Urologist Willett Whitmore neatly sums up the entire clinical dilemma that is prostate cancer<sup>[1]</sup>. The concept of "overdiagnosis" and "over treatment" as it relates to early prostate cancer is now widely accepted. One commonly used and useful, though scientifically imprecise, analogy, when talking to patients is that prostate cancers can either be "tigers" or "pussy cats".

In a brief survey of clinicians in the UK National Cancer Research Institute's prostate cancer Clinical Studies Group (Mason, unpublished), the distinction between the two was the most frequent item on the "wish list" that these clinicians cited. Conversely, for patients with metastatic prostate cancer, the most common cause of death - by some margin - is due to prostate cancer<sup>[2]</sup>. For patients with "significant" disease, and particularly those with metastatic disease, cure is currently virtually impossible, and there is an urgent imperative to improve treatment. The oft-repeated platitude that a man is "more likely to die with his prostate cancer than of it" is completely inappropriate for someone

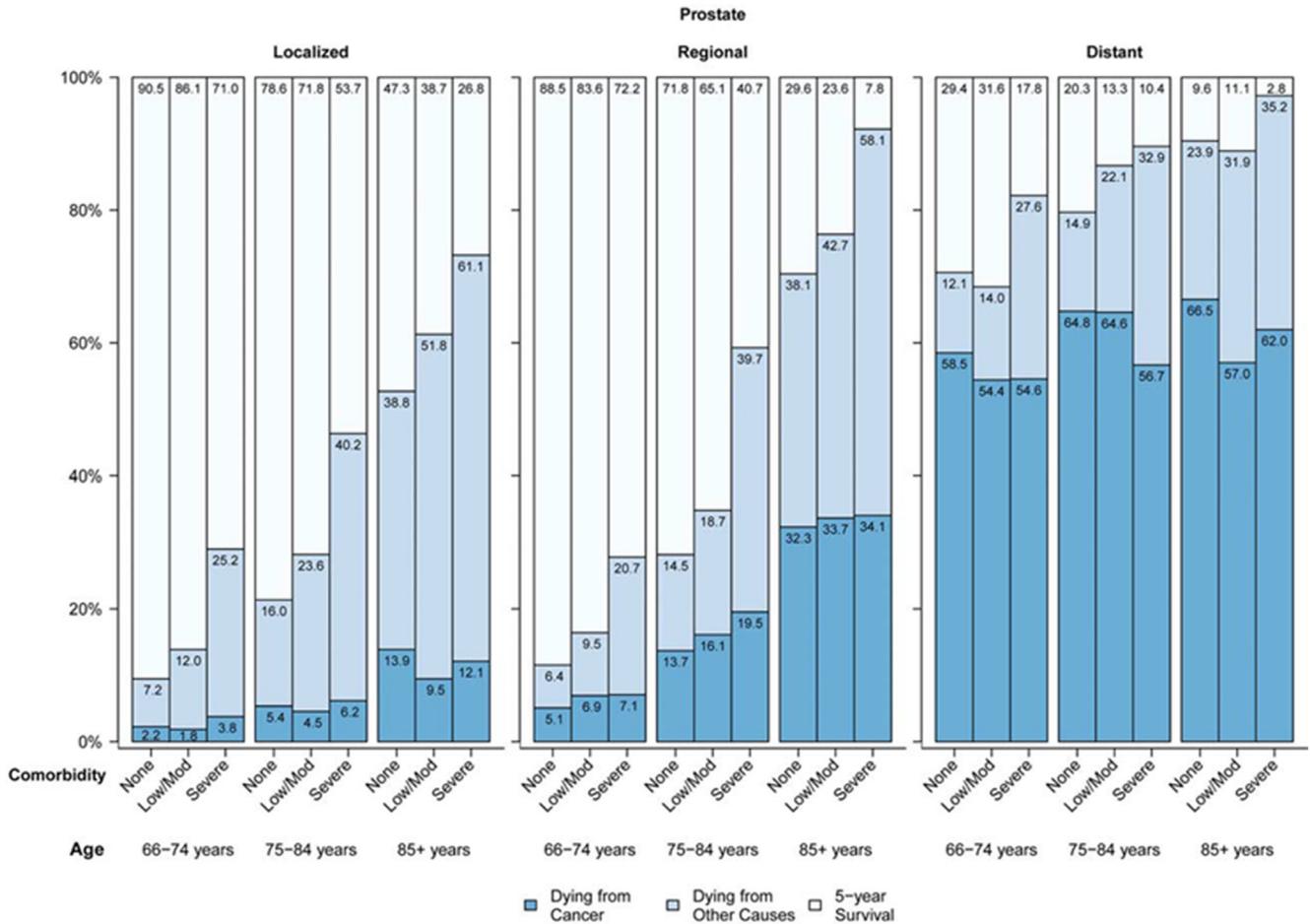


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**Figure 1:** Probabilities of dying from cancer, dying from other causes, and survival are stratified by stage, comorbidity status, and age among men who were diagnosed with prostate cancer between 1999 and 2005. Mod indicates moderate. (Reprinted with permission from Edwards *et al.*<sup>[3]</sup>)

with metastatic disease as illustrated in Figure 1<sup>[3]</sup>. For advanced (metastatic) disease, some form of hormone therapy, or more properly, androgen deprivation therapy (ADT), has remained the cornerstone of treatment. Usually this is given as luteinizing hormone releasing hormone (LHRH)-agonist injections, which decrease testosterone levels by virtue of their strong affinity for the LHRH receptors in the pituitary, preventing native LHRH from binding. More recently, other approaches have been developed, including orally administered drugs which bind antagonistically to the androgen receptor.

### LOCALISED PROSTATE CANCER - WHO NEEDS TREATMENT, WHO CAN BE TREATED?

Treatment for “early” prostate cancer, that is, cancer confined to the prostate and entirely within the gland, tends to fall into three main categories: surgery, radiotherapy, or active surveillance. The last of these

deserves some explanation; its philosophy is based on the assumption that if a patient harbours an indolent cancer (a “pussy cat”), it would be safe to monitor him carefully, but to defer curative treatment until and unless there is evidence that his disease is progressing. In the absence of firm evidence, there has always been a tendency for specialists to recommend their own treatment modality to a patient<sup>[4]</sup>. Efforts to establish which of the two major options - surgery or radiotherapy - is superior were unsuccessful for decades, and in the vacuum created by the lack of evidence, unsubstantiated opinion was present in abundance. However, this has changed recently with the publication of the first results of the UK ProtecT trial. In this trial, 1,643 patients with early prostate cancer were randomly allocated to treatment with surgery, radiotherapy, or active monitoring (a slightly different approach to active surveillance in that in the latter, often includes a re-biopsy of the prostate after a few years<sup>[5-7]</sup>). After a median follow-up time of 10 years, the trial allows clinicians to make several important

observations:

1. Very few patients, of the sort selected for this trial, die of prostate cancer, a least over a 10 year period. It should be stressed that the patients in this trial had early, localised disease, apparently confined to the prostate (categorised as stage cT1-2, N0, M0). Prostate cancer-specific survival rates in all 3 arms of the trial were 99%.
2. The outcomes after surgery and radiotherapy were the same, and both treatments were roughly equivalent in the degree to which their side effects affected quality of life.
3. However, more patients managed by active monitoring suffered progression of their disease, including the subsequent development of metastatic disease, though this has not, yet, translated into a worsening of their 10-year overall survival rate. It should also be stressed that, although the numbers progressing after active monitoring were double the numbers after surgery or radiotherapy, the absolute excess was only of the order of 4%.

Looking at the patients who died of prostate cancer, one might reasonably expect to have been able to pick them out retrospectively, based on the conventional clinical parameters of tumor stage, prostate-specific antigen level, and Gleason grade. Unfortunately, such complacency would be misplaced. For example, of 17 patients who died of prostate cancer, 8 had Gleason scores of 6 at diagnosis, and 9 had scores > 7. The numbers are very small, and some patients with apparently Gleason 6 could have had more aggressive tumors missed due to sampling errors, some of which might have been identified on modern imaging such as multi parametric magnetic resonance imaging, which among other things is capable of detecting anterior tumors that might not have been biopsied in this cohort. Even so, it seems inconceivable that these clinical parameters, which we use to stratify patients into “low”, “intermediate”, and “high” risk groups, are sufficient to enable us to determine which patients with early prostate cancer need treatment, and which ones do not. This is a major, and urgent clinical priority - solving it would, among other things, revolutionise the approach to prostate cancer screening. As described by Maitland in an accompanying answer in this themed issue, the scientific answer to the question of how to distinguish tigers and pussy cats will not come from cell lines, but will require a combination of biobanking of tissues from patients with early prostate cancer, combined with meticulous collection of associated clinical outcome data. Without the latter, the former are

rendered relatively meaningless in this context.

Turning to a different category of prostate cancer, locally advanced disease (where the cancer has spread beyond the capsule of the gland, or into the adjacent seminal vesicles, but no metastatic spread), the prevailing clinical bias was different. Early studies had already shown that, in the context of “old fashioned” radiotherapy, outcomes were less good than for localized disease. In retrospect, many patients who were then labelled as “locally advanced” might today be recognised as having still more advanced disease. The pivotal study by the European Organisation for Research and Treatment of Cancer (EORTC) showed that the addition of ADT to radiotherapy substantially improved survival<sup>[8]</sup>, but it left an open question about the role of radiotherapy. Nihilists argued that patients with locally advanced disease actually had occult metastatic disease, and that the important modality was the ADT. This was refuted in two randomised trials, of similar design, in which patients with - predominantly - locally advanced disease (some had high risk localised disease) were randomly allocated to ADT alone, or to ADT plus radiotherapy<sup>[9,10]</sup>. These trials showed unequivocally that radiotherapy - a locally directed, potentially curative treatment, improved survival. This probably means that some patients with locally advanced disease can be cured with local treatment. Moreover it means that as a group they do, indeed, “need” to be cured - but we should not forget that other explanations leading to improved survival without “cure” are not impossible.

After more than two decades, we can begin to answer Whitmore’s questions: for patients with early prostate cancer, cure is apparently not necessary in many cases, at least over a 10-year period. Our dilemma is now that, though we know that this does not apply to all such men, we do not know how to identify the all-important minority of such men who do need treatment. Two other studies, previously published, have randomised patients to surgery, or to “watchful waiting”<sup>[11,12]</sup>. The Swedish study reported improved survival with surgery, but the benefits appear to be restricted to patients under 65 years of age. The American study showed no evidence of a survival benefit overall, though suggested some benefit in some men in a higher risk category. In contrast, the studies of locally advanced disease not only show that this category of disease is both life-threatening and yet curable, but they also point to a category of disease which is deserving of more basic scientific attention than perhaps it has had. All these studies carry the same implication: the need for better biomarkers to enable us better to stratify patients. To test this

hypothesis a lab programme which compared tissue from early disease with those from locally advanced disease would surely bear fruit?

## WHAT HAVE WE LEARNED FROM CLINICAL TRIALS ABOUT LIFE-THREATENING PROSTATE CANCER?

Generations of oncologists and urologists in training were taught that advanced prostate cancer was characterised by a phase during which the disease would respond to hormone therapy of some sort, an observation that dates back over 70 years<sup>[13]</sup>. After a period, which in the case of metastatic disease might have been only of the order of 18 months, the disease progressed, and it was perfectly reasonable to ascribe the label “hormone resistant” to this latter phase. A “favourite” question that clinicians want to ask of their scientific colleagues is why this should be, and what might be the mechanism of disease progression after first line treatment with ADT. The multitude of explanations seem to fall into two categories: one in which some sort of acquired hormone insensitivity emerges, probably as a result of additional mutations, or other changes in key molecules such as the androgen receptor<sup>[14]</sup>. An alternative possibility is that disease progression results from the clonal expansion of a subgroup of cells, present at the time of the initial ADT, but insensitive to treatment *ab initio*. Support for the latter possibility comes from a randomised trial conducted by the EORTC, in which patients, who were not fit enough to receive curative therapy, were planned to commence long-term ADT and were randomised between immediate therapy, and treatment delayed until further disease progression<sup>[15]</sup>. There was no difference in prostate cancer mortality, though there was some improvement in mortality from any cause (the reasons for this are still debated). However, strikingly, the time course to the onset of disease progression after first line ADT, was identical, irrespective of whether the ADT was given immediately, or delayed<sup>[16]</sup>. Why might the time at which so-called “hormone resistant” disease is detectable be independent of when ADT was given? Almost the only explanation, if the findings are generalisable, is that resistant disease has emerged from a resistant sub-population that was present at the time of the initial therapy. Is this true? We need our scientists to answer this question.

Of the novel anti-androgens described above, one in particular deserves mention. Abiraterone acetate is an inhibitor of androgen synthesis, via dual inhibition of the 17 $\alpha$ -hydroxylase/C17,20-lyase enzymes, and it reduces testosterone levels in untreated men<sup>[17]</sup>. For

some years, this drug was, effectively, put “back on the shelf”, because it was not obvious what advantages it might offer compared to existing anti-androgens such as flutamide, although the mechanism of action is different; flutamide is a competitive blocker of the AR, while abiraterone inhibits androgen synthesis. Part of the reason for the clinical uncertainty was that in the late 1990s, when this decision was made, it was not appreciated that prostate cancer cells contained low levels of androgen, even in advanced cases, and that they were even capable of synthesising their own androgen<sup>[18]</sup>. Once this was recognised, there was a new rationale for testing abiraterone in patients progressing after firstline ADT. This was done in two pivotal randomised trials, comparing abiraterone with placebo and showing unequivocally that abiraterone improved survival<sup>[19,20]</sup>. As well as the obvious clinical benefits, these studies confirmed, and extended the initial laboratory observations; prostate cancer growth, even in advanced cases, remains driven by the androgen receptor. Mutations in the AR may allow cancer cells to respond to minutes levels of androgen, to different ligands, or even to be ligand-independent, but at its heart, advanced prostate cancer is anything but “hormone-resistant” - if anything, it is often “hormone super-sensitive”. This finding drove the recent change in nomenclature, from “hormone-resistant” to “castrate refractory”, a term which we must acknowledge is hated by our patients. We must also remember, though, that the survival benefits in these advanced patients are modest- of the order of a few months’ only, and that disease progression after abiraterone (and similarly after novel and more potent AR blockers such as enzalutamide) is inevitable<sup>[21,22]</sup>. The scientific imperative for clinicians is to understand what other pathways co-operate with AR-mediated signalling to drive subsequent disease progression.

One way to overcome the complex effects of multiple, diverse, and - within a tumor - heterogeneous mutations is to treat patients earlier in the course of their disease, and this was the thinking behind the STAMPEDE trial, which tests a number of additional therapies, given alongside first-line ADT. This has already borne fruit, with chemotherapy using docetaxel being recognised as the new standard of care, in combination with ADT, for patients with metastatic disease who have not yet had long-term hormone therapy, following reports from the STAMPEDE and CHARTED trials that docetaxel given at this time improved overall survival with a 25% reduction in the odds of death<sup>[2,23]</sup>. Results from the addition of abiraterone to ADT in the STAMPEDE trial, and also in a second trial called LATTITUDE, are expected imminently. Many questions arise from these studies: what is the mechanism of the benefit showed by docetaxel? Which patients benefit, as surely not all

patients do so? Are there other agents which might be further combined?

## HOW CAN OUR SCIENTISTS HELP US TO BETTER TREAT OUR PATIENTS?

If we are to transform the treatment landscape for prostate cancer, clinicians and scientists must work together ever more closely. Prostate cancer defeats us when we do not accurately stratify patients according to their risk of dying of disease, when we fail to overcome the effects of tumor heterogeneity, and when our attempts at therapy spur further disease evolution and the emergence of new resistance mechanisms. At the same time, we over-treat men who in reality do not need it, and some of those men needlessly suffer long term side effects as a result. We have all recognised the need for the development of better biomarkers that will characterise disease states. I suggest that as clinicians we have a duty to help our scientific colleagues, especially focusing our efforts on several areas:

1. The various and peculiar clinical phenomena which we observe in our patients, through clinical trials, and clinical observations. Another critical observation has been the emergence of new patterns of disease, maybe following the selection pressures on tumor cells resulting from more diverse and novel therapies.
2. The provision of tissue and blood samples in a meaningful way. Samples from patients are usually characterised in the crude terms that we use in the clinic; but, for localised disease, what do the terms “low risk”, “intermediate risk” and “high risk” actually mean? The data from the ProtecT trial, though from very small numbers of dying patients, argue that these terms are no guarantee that scientists will really be studying cells that are indolent, or aggressive, if they use samples based on these labels. The best we can say is that tumors that are “high risk” are more likely to harbour cells with metastatic potential than say tumors that are “low risk”. We know that prostate cancers are often multifocal, and heterogeneous; how do we overcome this? Perhaps circulating tumor products, including but not restricted to circulating tumor DNA, will in time give some sort of precis of the profile of a tumor population. What about tumor evolution? This would argue for repeated sampling in order to give a longitudinal profile of tumor behaviour. This does, however, carry some significant implications

for patients; biopsies from metastatic sites may need special procedures such as computed tomography-guided biopsies; they may be unpleasant - biopsy in bone is notoriously painful and may even require hospitalisation or a general anaesthetic, especially, if multiple sites are to be biopsied at the same time. As well as the ethical implications, the resource implications for the NHS are far from trivial.

3. Prostate cancer therapy, as with other types of cancer, must evolve from an era of empiricism, to the era of precision medicine<sup>[24]</sup>. The utopian vision, whereby a clinical sample somehow gets to the lab, and a subsequent analysis leads to a report that precisely determines the required treatment, will be difficult at best and maybe impossible to fully realise. It may not be helped if the laboratory analysis is based only on a random sample from a primary tumor, maybe taken years before the onset of metastatic disease, which is the objective of the study, though when such samples yield cells with the characteristics of stem cells, the insights can be striking<sup>[25]</sup>. Nonetheless, we may need to grapple with the practical, ethical, and clinical challenges posed by metastatic biopsies - and maybe not just once, but repeated during the course of a patient's illness, in order to get a profile of their tumor that reflects the current status at a time when therapeutic decisions are being made. If we can, in the future, safely and reliably inhibit multiple signalling pathways in tumor cells, then a more aggressive clinical approach to tumor sampling might be justified.

## DECLARATIONS

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M. Mason conceived the idea and wrote the manuscript.

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### Patient consent

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Not applicable.

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