Transforming the diagnosis and treatment of localised prostate cancer

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The current diagnostic and therapeutic strategy for localised prostate cancer is not working. In fact it is severely flawed and fraught with controversy. This has not been helpful to patients who are considering entering the diagnostic pathway or who have, inadvertently, found themselves within it. Due to the random nature in which we carry out prostate biopsies there is inaccuracy in detection, localisation and characterisation of cancers. Much debate has centred on these errors, but what is clear is that current principles of diagnosis and treatment lead to significant harm and little benefit. Despite a general acceptance that these problems are real and serious, few corrections have been put forward to help mitigate them. That is, until now.

The current strategy has arisen from our imprecise diagnostic pathway. We don’t know where the cancer is, so subject the prostate to randomly placed needles via a Trans Rectal Ultrasound (TRUS) Guided Biopsy in the hope of hitting the tumour. This leads to over-diagnose, under-diagnose, miss-classification of risk, and both over and under-treatment. If we do find cancer, we usually subject the entire prostate to radiotherapy or surgery, which damages surrounding structures like neurovascular bundles, the external urinary sphincter, rectum and bladder neck.

If the benefit of treatment was significant, then the resulting 10% chance of incontinence, 20% chance of impotence and 10% chance of rectal side-effects (pain, bleeding, diarrhoea) might be justifiable. The benefit of radical therapy is smaller however, and although treating intermediate and high risk localised prostate cancer in this way could be justified (c. 5% absolute risk reduction in mortality at 10-15 years), there seems to be no benefit in survival for low-risk disease.

Ultimately, TRUS biopsy performs poorly because it is conducted without knowledge of the cancer location.

Ultrasound is used simply to determine diagnosis clinically insignificant prostate diagnosed with prostate cancer, yet many patients are unnecessarily subjected to it.

Conversely, transrectal biopsies miss estimated false negative rate of one in three men, in community for yearly PSA testing, or the in years in one man.

Risks and Complications from Transrectal Biopsy

Infection
- Bacteriuria: 20%-50%
- Bacteraemia: 20%-70%
- Urinary tract infection: 1%-8%
- Life-threatening sepsis: 1-4%

Bleeding
- Haematuria: 50%
- Haematospermia: 30%
- Rectal bleeding: most

Urinary
- Acute urinary retention: 1%-2%
- Voiding symptoms: 10%
Systemic
- Vasovagal reaction 0%

Imaging is redefining our pathway

Magnetic resonance imaging can change all of this and improve the care we offer men. Multi-parametric MRI, (Figure 5), coupled with targeted biopsies, can rule out clinically significant lesions with a negative predictive value in the order of 90-95%

A number of trial groups have shown encouraging detection rates using multi-parametric MRI to target areas of suspicion. MRI can provide an accurate volume with indicators of higher Gleason grade prior to biopsy, and act as a bleb test to identify those men who require biopsies. This allows men with no clinically significant cancer to avoid entering the pathway, avoid having biopsies and potentially unnecessary treatment altogether.

Once an image is available, targeting a suspicious lesion accurately is crucial. A number of trial groups conducted targeted biopsies transrectally, again traversing contaminated mucosa. Until now the alternative, transperineal biopsies, have required general anaesthetic, carrying out 100,000 biopsies in the UK or 1 million biopsies across Europe under general anaesthetic is not feasible. However, subjective or transrectal biopsies is questionable when an alternative is available. My research group has been the first to show that transperineal targeted biopsies under local anaesthetic are feasible, tolerable and accurate. They can be carried out in clean non-theatre settings at low cost, with each procedure lasting only 20 minutes.

Multi-parametric MRI, Fig 5

Focal Therapy - Treating the tumour and not the whole prostate

Who should be referred for a pre-biopsy MRI and/or transperineal targeted biopsy at the Cromwell?

- Elevated age-specific PSA
- High PSA density 0.15ng/ml if a transrectal ultrasound volume has been calculated
- High PSA velocity 0.35ng/ml/year for PSA values <4ng/ml and 0.75ng/ml/year for PSA values >4ng/ml
- Elevated PSA with first degree relatives with prostate cancer and/or ethnic risk: eg. afro-caribbean/black men
- Normal PSA but abnormal free-to-total PSA ratio (defined by each lab but usually <25%)
- Men advised to have repeat TRUS biopsy following a previous negative biopsy due to persistent indication
- Men who are on active surveillance for presumed low risk prostate cancer
- Men considering minimally invasive therapies such as HIFU or cryotherapy

A dilemma awaits any man diagnosed with localised prostate cancer, as he will eventually be forced to choose between radical therapy or active surveillance. Radical treatment maximises the chances of cure, but comes with a 50% chance of serious impact on sexual and/or urinary function. Active surveillance, genito-urinary function is preserved in exchange for the psychological and healthcare burden of intensive surveillance.

Compared to other malignancies, prostate cancer is an outlier. Breast, renal, thyroid, liver, and pancreas all involve tissue-preservation therapies. If appropriate, which are dependent on location and the burden of cancer. These areas of oncological surgery developed tissue-preservation, as opposed to radical principles for wider surgical margins, due to improvements in diagnostic tools which are reliant on finding measurable disease which undergoes targeted sampling and treatment. The transrectal biopsy has done the opposite for prostate cancer. Random blind sampling has forced our hands as clinicians so that we have to apply radical whole-gland principles. But this is changing.

Studies show that it is sufficient to treat less than the whole-gland. This is called focal therapy, (Figure 6), and it leads to far less genito-urinary and rectal side-effects. There are currently two modalities approved by NICE in the UK for delivering focal therapy, high intensity focused ultrasound (HIFU) and cryotherapy. NICE have stated that focal HIFU and focal Cryotherapy for localised prostate cancer can be offered to appropriately selected patients subject to their informed consent, the notification of local clinical governance leads, and stipulation that all patients are treated within a clinical trial or entered into a prospective registry. Both of these mechanisms are now in place in the UK.

There is a clear consensus that focal therapy should only be applied for men who require and stand to benefit from treatment, and in that setting it retains the benefits of cancer control whilst reducing the side-effects significantly. Current data from over 3000 men treated internationally and 500 men treated in my own group shows that incontinence after focal therapy is 0-5% (radical therapy can lead to incontinence in 15-20%). Whilst erectile dysfunction occurs in 5-10% of men with good baseline function (radical therapy rates vary from 30% to 60%). Early to medium cancer control using biopsies after treatment shows between 80-90% have a successful treatment, with 10-15% of men requiring redo-treatment with minimal additional morbidity.

Conclusion

The current pathway for prostate cancer diagnosis and treatment is letting many men down. Recent advances in imaging and minimally invasive focal therapy mean that we can start to redress the balance so that the risk and benefits to men and their families is finally going in the right direction.

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