DIAGNOSIS AND TREATMENT OF PROSTATE CANCER

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 with 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-diagnosis, under-di
cancer, we usually subject the entire p
vascular bundles, the external urinary s

If the benefit of treatment was significa
chance of rectal side-effects (pain, ble
and although treating intermediate and
reduction in mortality at 10-15 years), t

Ultimately, TRUS biopsy performs poo
used simply to determine that the nee
clinically insignificant prostate cancer.
with prostate cancer, yet most of these

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

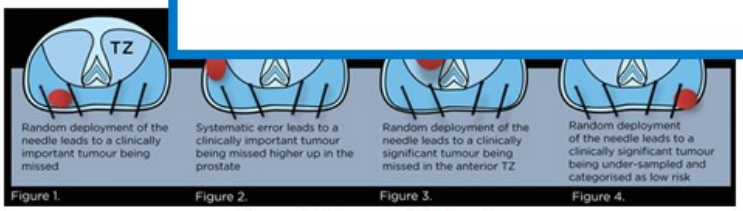

Figure 1-4: Transrectal biopsies

They can also be unrepresentative of the true burden of cancer, (Figure 4). One in three men deemed low risk on transrectal biopsies can have a higher volume or grade cancer, or both when a more accurate biopsy test is applied. The cancer risk attribution errors of transrectal biopsy result in inappropriate treatment allocation; men with high-risk disease might be recommended conservative management in contrast to radical therapy, and men with low-risk disease are recommended radical therapy 'just in case'.

Three-quarters of men report at least one minor complication after prostate biopsy:

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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 triage 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.

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 8%

Risks and complications from Transrectal Biopsies

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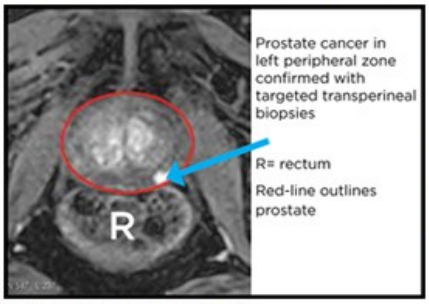

Figure 5: Multi-parametric MRI

Once an image is available, targeting a suspicious lesion accurately is crucial. A number of trial groups conduct 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 viable. However, subjecting a man to 'transfaecal' 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.

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/ml if a transrectal ultrasound volume has been calculated
- High PSA velocity. 0.35 ng/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 e.g. afro-caribbean/black men
- Normal PSA but abnormal free/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. With 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-preserving therapies, if appropriate, which are dependent on location and the burden of cancer. These areas of oncological surgery developed tissue preservation, as opposed to Halsted 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.

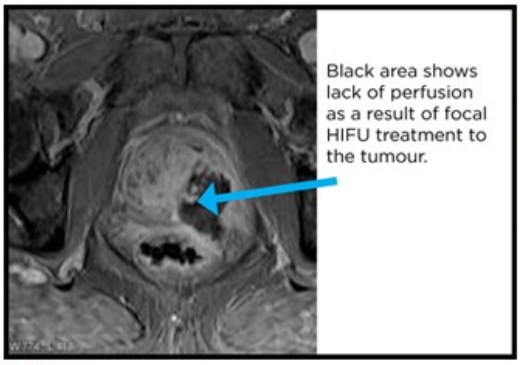

Figure 6

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 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 600 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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