

# The Modern Management of Localised Prostate Cancer

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## ***Introduction***

This is a personal reflection on the management of localised and advanced prostate cancer and relates to my 20 year experience in the management of this, the commonest cancer in men. The critical issue, in my view, is that the patient should have their disease diagnosed accurately and comprehensively in order to inform the decision on the best prostate cancer treatment for an individual. This requires a pre-biopsy multiparametric MRI scan followed by targeted (+/- MRI Fusion) and / or systematic transperineal biopsies. Once the diagnosis has been made the cancer can be cured or treated in a number of ways. The treatments offered depend on whether the patient has low, intermediate or high risk disease:

- |  |                          |
|--|--------------------------|
| ❖ Active Surveillance                    | Low Risk                 |
| ❖ Dynamic Prostate Brachytherapy         | Low / Intermediate Risk  |
| ❖ Robotic Prostatectomy (Da Vinci)       | Low / Intermediate Risk  |
| ❖ External Beam Radiation Therapy (EBRT) | Intermediate / High Risk |
| ❖ Brachytherapy Boost + EBRT             | Intermediate / High Risk |
| ❖ Robotic Prostatectomy +/- EBRT         | High Risk                |
| ❖ Hormonal Therapies                     | High Risk                |
- ❖ Focal Therapies including HIFU, Nanoknife (Electroporation) and Interstitial Laser Ablation remain experimental and are generally reserved for low risk or intermediate risk cancer within the context of clinical trials

All are very different modalities and it can be difficult to choose, however the management an individual receives will depend on whether they have :

- ❖ A low, intermediate or high risk for disease progression dependent on the PSA , the clinical Stage & the Gleason grade
- ❖ Significant lower urinary tract symptoms
- ❖ Significant co-morbidity, their age and their life expectancy
- ❖ A strong desire to preserve their erectile function
- ❖ Access to the resources to deliver advanced treatment modalities

## ***Dealing with the Diagnosis of Prostate Cancer***

The diagnosis of prostate cancer can be terribly emotive and have a major impact upon relationships and family. An element of depression and stress is a common feature and a very normal response to the diagnosis. It is absolutely crucial that you take time to reflect upon your treatment options as explained to you.

**Decisions should not be taken too quickly** and a focussed, reasoned, and calm attitude will be an asset in dealing with the pressures you will face. We are here to help you. Our multidisciplinary approach at London Bridge Urology ensures that you have the benefit of prostate cancer specialists, specialist urology nurses, physiotherapists and psychotherapists on hand to advise and reassure.

**Remember-** if a particular treatment doesn't feel right for you, then it probably isn't suitable. If a treatment feels right, then it probably is. Keep asking questions until you are satisfied. After studying all your options, spoken to the appropriate specialists, make use of the knowledge gained and trust your instincts.

**Be realistic.** If a man is not generally in good health or overweight, surgery may not be the best option. Surgery of any kind is hard, and recovery is easiest when a person is in good shape. If a man has bowel or bladder problems already, radiation of any kind may make them worse. Fortunately, for many patients, there are a number of other options, including various forms of targeted radiation therapies including Brachytherapy, IMRT and Cyberknife.

**The ideal treatment** for early prostate cancer would both provide an excellent chance of cure and minimal side effects with regard to urinary continence (leakage) and potency (erectile function). Unfortunately the ideal treatment does not exist (if it did then there would be no question about the benefit of cancer screening), all radical prostate cancer treatments can have significant side effects and an individual's options are dependant upon a number of interrelated factors:

## ***Comprehensive Treatment Programme***

A Comprehensive Integrated Localised Prostate Cancer Treatment Programme is essential to ensure that the management an individual receives is most appropriate for that person and his disease. A dedicated Prostate Service supported by Urology Nurse Specialists, Clinical Oncologists and Urological Surgeons with the back up of Specialist Pathology and Radiological services are the essential components. The Urology Centre at Guy's Hospital was the first department in the UK to introduce robotic surgery in to regular NHS service along side established laparoscopic, brachytherapy, radiotherapy and active surveillance

programmes. This breadth of experience is essential to our vision to ensure we offer the right treatment for the right patient. This vision of integrated care extends in to our private practice at London Bridge Urology.

Over the last 15 years, we developed such a multidisciplinary programme within “London Bridge Urology” at London Bridge Hospital, however integrating the specialist diagnostic facilities and the specialist treatment facilities for robotic surgery, brachytherapy and radiotherapy on to one campus has been a challenge. However since 2017, London Bridge Urology has been able to offer all prostate diagnostic and treatment procedures within a fully integrated multidisciplinary environment across the London Bridge HCA Hospital Campus.

### ***The Shard Outpatient and Diagnostic Centre and HCA@Guy's***

For many years the prostate cancer services provided by London Bridge Urology were fragmented. Robotic Prostate Surgery had to be carried out at other HCA facilities because there was no robot at London Bridge, whilst day case Brachytherapy was provided at the London Bridge Hospital, the External Beam Radiotherapy treatments were delivered within a dedicated HCA facility on the Guy's Hospital site, at the Harley Street Clinic or the Cyberknife Centre.

This all changed in 2016 when London Bridge Urology moved its outpatient and diagnostic services to a dedicated facility on the 6<sup>th</sup> Floor within the Shard Outpatient & Diagnostic Centre. We have a minimum of 8 well equipped consulting rooms available at all times to facilitate multidisciplinary clinics.

Within the Specialist Urology Outpatient Centre there are facilities for urinary flow rate & residual urine assessments. There are two excellent treatment rooms for minor procedures including prostate biopsies, flexible cystoscopy and we can provide “in house” ultrasound, supported by a dedicated uro radiologist. Phlebotomy services for routine blood tests are available from 8am on the floor and with turnaround times of less than 4 hours, routine results including PSA tests are available on the same day. On the 5<sup>th</sup> Floor of the Shard there is a superb Diagnostic Imaging facility with state of the art, 3T MRI scanning, CT scanning and ultrasound. Prostate MRI scans can be done in the morning, reviewed on the HCA PACs system immediately and reported within 4 hours.

In April 2017 all the Urology Inpatient and Operating Theatre services of London Bridge Hospital were concentrated in to the new HCA private inpatient / theatre complex located on the top 4 floors of the Cancer Treatment Centre on the Guy's Hospital site. The theatres are equipped with the most modern Da Vinci Xi Robotic Surgery System with dual console, urological lasers for prostate and stone disease and integrated endourological SMART theatres.

The initiative to develop the facilities at London Bridge has provided the opportunity to expand and improve the integration of prostate cancer diagnostic and treatment pathways across the HCA@Guy's campus. The services provided by London Bridge Urology have been enhanced by the expansion of these facilities and we are able to provide a comprehensive multidisciplinary package of care to patients from diagnosis to effective treatment, all within one campus.

### ***Robotic Radical Prostatectomy (DaVinci) – a potted history***

Robotic Assisted Radical Prostatectomy was popularised by Mani Menon of the Vattikuti Institute in Detroit and offered the advantages of the laparoscopic approach (better vision, reduced bleeding, better nerve preservation, less analgesia and reduced length of stay) with the enhanced dexterity of the endowrist offering 360 degree intuitive movement. For this reason the procedure has gained increasing popularity in the USA and now in Europe & the UK.

When we introduced robotic surgery to the NHS in 2005, it was supported by a major grant from the Guy's & St Thomas' Charity. Clinical governance issues required that we adopt a progressive stepwise approach to both the evaluation of the robot and its introduction into our surgical practice. Following observation visits to the Vattikuti Institute in Detroit we underwent robotic surgical training at a Surgical Skills Laboratory in Paris. We conducted regular training sessions with the Robot and carried out cases with surgical mentors from Detroit and the Cleveland Clinic in Ohio before beginning our own programme. Robotic urological surgery has now become routine in our department. We now carry out over 350 robotic cases each year at Guy's Hospital. Robotic surgery is carried out predominantly for prostate cancer, but also kidney & bladder cancers as well as for some benign conditions. There is no doubt that Robotics is the surgery of the future and our experience confirms this. At Guy's Hospital we were the first NHS hospital to introduce a dedicated robot for urological surgery. We have been using the robot since 2004 and our experience extends to over 3000 patients.

### ***My Experience of Robotic Radical Prostatectomy***

This is now the most commonly reported operative approach in the UK's BAUS Radical Prostatectomy Dataset. It is recognised that the highest volume surgeons achieve the most consistent results. I have experience of over 800 Robotic Radical Prostatectomies since 2006 and over 300 open radical prostatectomies before the introduction of robotic surgery. I am in the top 10 highest volume surgeons in the UK (BAUS Radical Prostatectomy Dataset 2018). Many other high volume surgeons offer only radical prostate surgery but my experience is not just limited to radical surgery. I have also carried out over 1000 prostate brachytherapy treatments for low risk prostate cancer and over 1000 Holmium Laser Prostate Enucleations, many in patients on Active Surveillance with concomitant benign prostate enlargement and others with very large prostates who

following surgery have a prostate of normal size and are then in a better position to have effective radiotherapy treatment. This is particularly suitable in the over 70s where radical surgery in very large prostates can be associated with greater risks of incontinence. My recommendations for treatment are based upon my clinical experience are determined by the individual needs and how these relate to their disease. I aim to provide with my colleagues a multidisciplinary assessment and recommendations for a bespoke treatment plan rather than a one size fits all.

### **NeuroSAFE Procedure**

This is an intraoperative assessment of the surgical margins at the time of a robotic prostatectomy and augments our ability to preserve the nerves safely, particularly in cases where we might be concerned that the cancer is pushing close to the edge of the capsule on the MRI scan or where the biopsies are positive close to the capsular edge with evidence of perineural invasion. It provides immediate information on the pathological margins in relation to a nerve sparing procedure. After the nerve dissection has been completed and the prostate has been removed, it is handed to a pathologist who carries out a “frozen section” of the margins. If, having spared the nerves, cancer cells are seen at the prostate margin, the nerve can be resected on the affected side. Overall the procedure cannot guarantee negative margins but it probably allows nerve preservation in 50% more patients. The critical thing is to ensure that the MRI and biopsy pathology has been carefully reviewed pre-operatively. In some cases it may be clear that a nerve sparing procedure is not appropriate and the safest approach is a wide excision of the “at risk” area and concentrate on the nerve spare on the non-affected side.

### **“Retzius Sparing” Radical Prostatectomy**

“Retzius Sparing” surgery refers to the preservation of the structures anterior to the prostate itself. These structures include the ligaments which support the bladder neck and urethra promoting urinary incontinence. The procedure was developed as a method in which the prostate is dissected out from within these structures preserving the continence mechanism. It is being popularised as a method to improve the early continence following a radical prostatectomy, however available data from randomized controlled studies suggest whilst patients may leak urine less in the first six weeks after radical prostatectomy, in the longer term the degree overall continence is similar.

The early reports on the clinical studies of the surgeons using the technique show an increased rate at which cancer is found at the edge of the resected prostate, a positive surgical margin. The reported positive margin rates are 16.7 % with “Retzius Sparing” versus 7.7 % with a standard technique for cancer confined to the prostate (T2) and 31.8% vs 14.3% once the cancer had started to invade through the capsule of the prostate (T3). The presence of positive margins does not always mean that the cancer has not been cured but 50% of patients with positive surgical margins will need to have additional

treatment, such as radiotherapy or hormones. In most instances this risk is predictable and avoidable and if you are considering “Retzius Sparing” surgery you need to be confident that your disease is suitable, patient selection is paramount.

“Retzius Sparing” is not suitable for people who have significant anterior disease on MRI scan or biopsies. It is only really appropriate for small low grade cancers, the sort of cancers which may be perfectly well managed by Active Surveillance or brachytherapy. Most of the benefits of “Retzius Sparing” surgery can be achieved by carrying out most of the procedure using a posterior approach in which one is better able to mobilise and preserve the nerves and most of the dissection can be completed, preserving the anterior structures but ensuring that the ability to adequately excise tissue at the anterior and bladder neck margins are not compromised. This is the approach that I prefer, simply because in my view cancer control is paramount, incontinence is rarely a significant problem.

### **Urinary continence rates**

It is understandable that this is the greatest concern for patients however overall the outcomes are excellent and over 95% patients achieve complete urinary control, with no pad by one year. 50 % of patients may expect to achieve immediate urinary control following catheter removal and 70% within 2 – 4 weeks of the surgery, 30% of patients will have some leakage requiring pads for between 6 to 12 weeks. The remaining 15% regain control over a longer period.

The degree of incontinence observed varies with the extent of surgery required. Those with high risk disease requiring a wide excision and nodal dissections should expect to have urinary leakage for longer. Patients with lower risk cancers who are able to have full nerve sparing or are considered suitable for Retzius sparing surgery will tend to have an earlier return of urinary continence, however it should be recognised that this type of surgery is not appropriate for all patients, particularly where there may be a risk of positive margins because of the extent of high risk disease. The symptoms of patients with persistent incontinence can be improved with a combination of targeted pelvic floor exercises and or medications. Rarely an artificial urinary sphincter may be required to achieve continence, most commonly after a salvage radical prostatectomy following failed radiotherapy or brachytherapy treatment.

### **Erectile Function Post Surgery**

Even after bilateral nerve sparing radical prostatectomy the erectile function will always be compromised to some extent. Obviously this is an important factor but it should not be the priority when considering robotic prostate surgery, cancer control and continence are paramount. Increasing experience of the nerve sparing approach in selected patients

with the introduction of keyhole techniques with robotic assistance, the Retzius Sparing approach and the use of intra-operative frozen section (the Neuro-safe procedure) have improved both short & long term outcomes for erectile function. The most important factor is that patients should participate in an active rehabilitation programme and that they are well counselled before hand. Initial management may include the use of vacuum pump devices, injection therapies as medical treatments such as Viagra & Cialis are not always helpful in the first 3 – 6 months. Patients will often show continued improvement up to 3 years following surgery, supplemented by medication.

### ***Laparoscopic Radical Prostatectomy***

Laparoscopic Radical Prostatectomy has a long learning curve and the need for specialist training in the technical aspects of the surgery before embarking on a programme is essential. There are no advantages over the laparoscopic robotic approach. At Guy's, the robotic assisted approach replaced standard laparoscopic prostatectomy as our procedure of choice in 2009.

### ***Open Radical Prostatectomy***

The open radical prostatectomy is a well-described and reproducible technique with very few major complications reported. However, with the introduction of laparoscopy and robotic surgery, the indications for an open radical prostatectomy are increasingly limited. In my experience it is those patients in whom the laparoscopic robotic assistance approach proves impossible. At Guy's Hospital where we have done over 3000 radical prostatectomies this has only been necessary on a couple of occasions. The need for blood transfusion, post-operative pain relief and the risk of wound infection remain significant issues. Nonetheless it remains the Gold Standard against which all other treatment modalities must be compared. I am one of the few surgeons in the UK to have the experience to carry out open prostate surgery should this ever be necessary.

### ***Dynamic Intra Operative Prostate Brachytherapy***

#### ***(Potters' Technique)***

Brachytherapy for patients with early and low risk prostate cancer is a very attractive alternative to radical surgery and radiotherapy for many patients, with comparable relapse free survival rates as radical surgery at 10 years. Simplistically, this is the targeted insertion of titanium seeds impregnated with radioactive Iodine ( $I^{125}$ ) directly in to the

prostate to achieve a high dose to the cancer. At Guy's Hospital we were the first group in the UK to introduce this Single Stage dynamic approach. Louis Potters, who developed the technique at the Memorial Sloane Kettering Cancer Center, mentored our own programme. The seed implant is carried out under real time ultrasound with intra-operative dosimetry. This provides immediate feedback on the quality of the implant and allows us to maximise the dose to the prostate whilst minimising the dose to the urethra, bladder and rectum. We have treated over 800 patients at Guy's since December 2003 and with our private practice an experience of over 1000 patients.

The procedure is conducted as a single visit day case, no catheter is required and patients can return to work in a day or two. Urinary control is excellent although most patients will experience some frequency and urgency this is rarely a significant problem and is minimised by careful patient selection. Erectile function is very well preserved when compared to the alternative options such as nerve sparing radical surgery or hormone radiation. The procedure has been extremely well tolerated and 96% of patients are discharged within 16 hours of the implant. The urinary side effects can take 3 – 6 weeks to develop but many patients experience no immediate morbidity and can work or travel as normal.

### ***Focused Brachytherapy Implants vs Focal Therapies***

With improvements in the diagnostic pathway, specifically the use of pre biopsy MRI combined with targeted and systematic transperineal biopsies we are able to identify patients who may have predominant disease located within a particular area of the prostate. In these individuals it may be possible to consider whether they may be suitable for Focal Therapy. Many focal therapy treatments such as HIFU and the Nanoknife (electroporation) assume that only the index or focal lesion requires actual treatment. An assumption is made that low risk disease (Gleason 3+3) elsewhere within the gland can be safely observed and followed by MRI. This assumes that all the significant disease has been identified at the initial biopsy but in my experience of over 500 MRI Fusion targeted and transperineal biopsies less than 15% of patients appear to have true focal disease confined to one quadrant, over 30% of patients have disease in the other quadrants and it is a multifocal disease in over 85% of cases.

Focal brachytherapy is probably the ideal approach for focal treatments however we prefer to treat the whole gland as well as the target lesion. We preferentially “focus” the radiation dose to the most involved quadrant and we call this a “focused” brachytherapy implant. It works very well.

## ***Brachytherapy for Large Prostates and Previous TUR Surgery***

It is often said that brachytherapy is not possible in patients with larger glands or previous prostate surgery, this is not the case. The other major advantage of Potters' intra-operative dynamic approach is the ease with which it can be adapted and applied to patients with large prostates. Many centres would have difficulty treating these cases and would have to give many months of hormones to shrink the prostate beforehand, with a consequent worsening of the side effect profile. We have also implanted, with out difficulty or early complications, patients who previously had transurethral prostate surgery (TURP).

## ***Combination Brachytherapy and External Beam Radiation***

In those patients with higher risk prostate cancer, Gleason 4+3 or greater the option will often lie between radical surgery with a 15% chance that additional radiotherapy may be required or deciding that the risks of surgery in the more comorbid or elderly patient may not be appropriate. In these situations the combination of a focused brachtherapy implant followed by external beam radiotherapy will have comparable outcomes as surgery at 5 and 10 years with less risk of urinary incontinence. Longer term data would suggest that the cure rates are comparable and in my view no patient with locally advanced prostate cancer should submit to surgery without at least considering this option and the benefit of a multidisciplinary opinion with one of our radiotherapy colleagues.

## ***SpaceOAR (Rectal Spacers) in Radiotherapy / Brachytherapy***

The use of a rectal spacer, the SpaceOAR, a gel matrix product which is designed to separate the prostate from the rectum by at least 1 cm for up to 6 months has been shown in randomised controlled trials to reduce the incidence of radiation related bowel side effects from 5 % (1 in 20) to 0.5% (1 in 200). The procedure is recognised by NICE and although it is not freely available on the NHS, it is generally covered as an additional procedure by Insurance Companies. It is a simple and safe procedure carried out either after the placement of Fiducial Markers for radiotherapy or Cyberknife targeting systems or after a brachytherapy implant. It is very well tolerated and the benefits are obvious.

## ***High Intensity Focussed Ultrasound (HIFU) & Electroporation - the "Nanoknife" and Interstitial Laser Ablation***

These are minimally invasive approaches to treat prostate cancer which use ultrasound guidance correlated with MRI abnormalities to deliver a high intensity of focused ultrasound or electrical current to the prostate in segments. It can be used as both a primary treatment and as salvage treatment after radiotherapy. Whole gland treatment with these approaches, particularly HIFU are now considered suboptimal and these

treatments are now considered suitable only as a focal treatment for patients with very localised focal disease. The problem is that most patients with prostate cancer have multifocal disease. It is essential that patients be very carefully evaluated for their suitability for focal therapy by having proper transperineal targeted and systematic biopsies to identify the distribution of both MRI visible and MRI invisible disease. In my experience of over 500 MRI Fusion targeted and systematic transperineal biopsies true focal disease confined to one quadrant occurs in less than 15% of patients. 85% have additional disease outside the lesion but in the same quadrant and in 30% this was in other quadrants in what appeared to be normal prostate on the MRI. The procedures are usually done under a light general anaesthetic and some patients may require a limited resection of the prostate (TURP) at the time of the procedure to prevent urinary retention. The long term data with these treatments is limited but the best available suggest that about 70% of patients with “low risk” disease will be free of disease at 5 – 10 years, compared to over 95% of “low to intermediate risk” patients treated with radical surgery or brachytherapy. Nonetheless these are options to be considered in selected patients with very focal disease who would be unfit or unsuitable for more standard treatments.

### ***Conclusions***

Treatment advances in prostate cancer are dependant upon a multidisciplinary approach and the resource to invest in new technology. Our department has been more fortunate in this regard than others and I believe, we have the most comprehensive and integrated treatment programmes available in the UK . In some respects, this makes it harder to advise patients when the choice is so broad but I would rather that patients were well informed on their options. Most often, it is not which treatment would be best for an individual but why one particular choice would be a bad idea. We are here to help you in that decision.

**Rick Popert, London Bridge Urology, June 2018**