# HOW I TREAT: PROSTATE CANCER WITH MINIMALLY INVASIVE TECHNIQUES

**Mr Ricardo Soares, Prof Christopher Eden**

*Department of Urology, Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK*

Currently, 17-35% of newly diagnosed cases of prostate cancer (PrC) are classified as high-risk. This group of patients has the highest rate of metastasis and cancer-related death, making management of high-risk prostate cancer (HRPC) a top priority for improving PrC outcomes. We will then focus this discussion on our management of HRPC.

Following the introduction of prostate-specific antigen screening into clinical practice in 1980, there was a stage-migration of newly-diagnosed PrC cases towards more localised disease. However the Surveillance, Epidemiology, and End Results database shows that the incidence of pT3a disease has remained relatively constant throughout the past 15 years. Between 2000 and 2008, a period when urologists were more prone to operate on low-risk cases, 52% of our laparoscopic radical prostatectomy (LRP) patients were low-risk and only 18% were high-risk. An analysis of our cases from 2013-2014 shows a significantly different profile: 21% low, 50% intermediate, and 29% high-risk patients. We also consider surgery an option for locally advanced PrC patients as part of a multimodality treatment. Furthermore, as shown in the National Prostate Cancer Audit regarding patients from 2006-2008, almost 40% of locally advanced PrC patients in our Cancer Network received local treatment, either in the form of radical prostatectomy (RP) or external beam radiotherapy +/- brachytherapy.

Over the past years, multiparametric magnetic resonance imaging (mMRI) of the prostate has gradually evolved, with special interest on diffusion-weighted imaging (DWI) given that PrC areas seem to have lower apparent diffusion coefficient than benign areas. As recognised in the European Association of Urology (EAU) guidelines, mMRI has shown to have excellent sensitivity for detecting aggressive Gleason >7 cancers and is especially useful in detecting anterior tumours, commonly missed on transrectal ultrasound-guided (TRUS) biopsy. The same guidelines recommend that mMRI be done if it can trigger a (targeted) repeat prostate biopsy. In our Cancer Network, the majority of patients have an mMRI as a pre-biopsy triage, the result of which will determine if a biopsy is indicated. Any areas with prostate imaging-reporting and data system score 4 or 5 trigger a targeted biopsy with a template biopsy of the remaining prostate. This will be done transperineally if there is a need to sample the anterior part of the prostate. Patients with palpable disease may go directly to a TRUS biopsy and have a MRI or computed tomography for staging. All high-risk patients will also have a bone scan.

Traditional staging with digital rectal examination has shown to be inaccurate. While not consensual, it seems that mMRI, and especially tesla 2-weighted imaging, may be useful in staging selected patients with intermediate-to-high-risk PrC. Despite low sensitivity to detect focal (microscopic) extraprostatic extension, and MRI sensitivity, specificity and accuracy for detection of more extensive pT3a disease rises to 62%, 95%, and 88%, respectively, and may be even higher with DWI.[1] EAU recommendation is to use multiparametric MRI only in intermediate or high-risk PrC and if it can change patient management. Most of our patients have mMRI before prostate biopsy, so even low-risk patients have an mMRI at the time of decision on management. This is important, as mMRI with DWI seems to have a role in reducing positive surgical margins (PSM) caused by inadequate nerve-sparing surgery (NSS) by predicting extraprostatic extension. Initially, in our group, neurovascular bundle preservation was being carried out only in potent men with low/intermediate-risk disease and no palpable tumour on the side of the nerve preservation. This has gradually changed to include men with erectile dysfunction with the aim of improving continence, palpable disease (leading to incremental preservation), and high-risk patients if the location of the cancer permits it. Currently our only absolute contraindication for NSS is

suspected T3 disease on the side of the nerve spare. Our LRP series has shown that overall PSM rate correlates with pathological T stage but is not influenced by NSS.

Since starting to perform LRP in 2000, the technique done by this group has evolved in many ways. Nowadays, only low-risk patients have extraperitoneal LRP. D'Amico intermediate and high-risk patients have extended pelvic lymph node dissection (PLND) done transperitoneally to minimise the risk of lymphocele and enable easier access to the common iliac artery bifurcation for higher lymph node (LN) yield. Over the years, other adjustments to the surgical technique were made that reduced complications: nerve-sparing surgery with bipolar diathermy gave place to titanium clips to minimise thermal injury; closure of large port sites with Endo Close™ prevented hernias; and padding of arms prevented ulnar nerve neuropraxia. On the other hand, even without administration of prophylactic low-molecular-weight heparin, only four patients (0.4%) had thromboembolic events, which is in line with most European and American referral centres. This leads us to believe that early mobilisation and use of compressive stockings is sufficient for most patients post-operatively.

Contrasting with the discussion in intermediate-risk PrC, there is a consensus that PLND is indicated in HRPC, as the risk of nodal disease is significantly higher and PLND provides important information for prognosis that cannot be matched by any other staging tool. It is now clear that PLND should be done following an extended template, as 19-35% of positive LNs are exclusively outside the area of standard PLND. Therefore, we perform extended PLND including the common iliac nodes up to the ureteric crossing and the nodes medial and lateral to the internal iliac artery. The next step in the development of our technique will be to include the presacral area for high-risk patients, which should reduce the incomplete clearance of nodes to 3%. In our series, the replacement of standard PLND by extended PLND in 2008 led to a 3-fold increase in LN yield and a 10-fold increase in the rate of detection of LN involvement. The cases done in 2013-2014 had a median LN yield of 17 (range 5-37) and a 27.3% rate of node-positivity, which is a result of the profile of the PrC patients operated at our centre.

It is important to know if there is nodal disease, but it has also been shown that considering the number of positive nodes enhances the predictive accuracy of nodal staging (60.1-65.0%). Briganti et al.[2] reported that patients with up to two positive nodes on extended PLND (ePLND) have significant and better long term cause-specific survival (CSS) than the ones with three or more (84% versus 62% at 15 years; p<0.001).[2] The same type of conclusion came from a study by the University of Bern group, where the progression free survival was significantly higher for patients with only one positive node (38.5%) when compared with the patients with two or more positive nodes (12.2%).[3] The same study found that the number of positive nodes significantly affected the time for biochemical recurrence, symptomatic progression, and cancer-related death. It is our belief that there will soon be enough evidence to change the tumour, LN, and metastases staging classification for prostate cancer in order to divide node-positive patients into N1 and N2 depending on the number of positive nodes, as they carry different prognosis.

Besides its prognostic importance, PLND seems to play a role in improving survival. Level 1-evidence of PLND's therapeutic benefit came from a randomised prospective study of 360 consecutive patients receiving extended versus standard PLND. After a median follow-up above 6 years, they concluded that an extended PLND increased biochemical PFS in intermediate (73.1% versus 85.7%; p=0.042) and high-risk patients (51.1% versus 71.4%; p=0.036).[4] Several studies corroborate that RP with ePLND may be an option for node-positive patients, especially in case of oligometastatic nodal disease. Studer's group published a study on a series of 122 consecutive node positive patients with no neoadjuvant or adjuvant androgen deprivation therapy (ADT). They reported a 10-year CSS of 78.6% for patients with two or fewer positive nodes and 33.4% for three or more nodes (p<0.001). Once again, the number of positive nodes (HR=1.38; p<0.001), ≥3 positive nodes (HR=5.64; p<0.001), high pathologic tumour stage (HR=4.05, p=0.021), and high pathologic Gleason grade (HR=2.42, p=0.02) were significant predictors of negative outcome.[5] Following these data, EAU guidelines consider ADT to be the treatment of choice for patients with more than two positive nodes on ePLND, irrespective of having RP or radiation therapy. They also recommend that ADT monotherapy should only be given to patients who are unfit for any type of local therapy. In accordance to this, we offer LRP with ePLND as an option for patients with limited nodal disease as a part of a multimodality approach.

In conclusion, times are changing for RP. Fewer low-risk patients are being operated on, but RP has been shown to improve outcomes in high-risk localised, locally advanced, and oligometastatic nodal PrC. New clinical trials may even extend these boundaries to oligometastatic bone disease. In any situation, it is important that the patient is aware of the specifics of surgery in HRPC and the possible need for multimodality treatment.

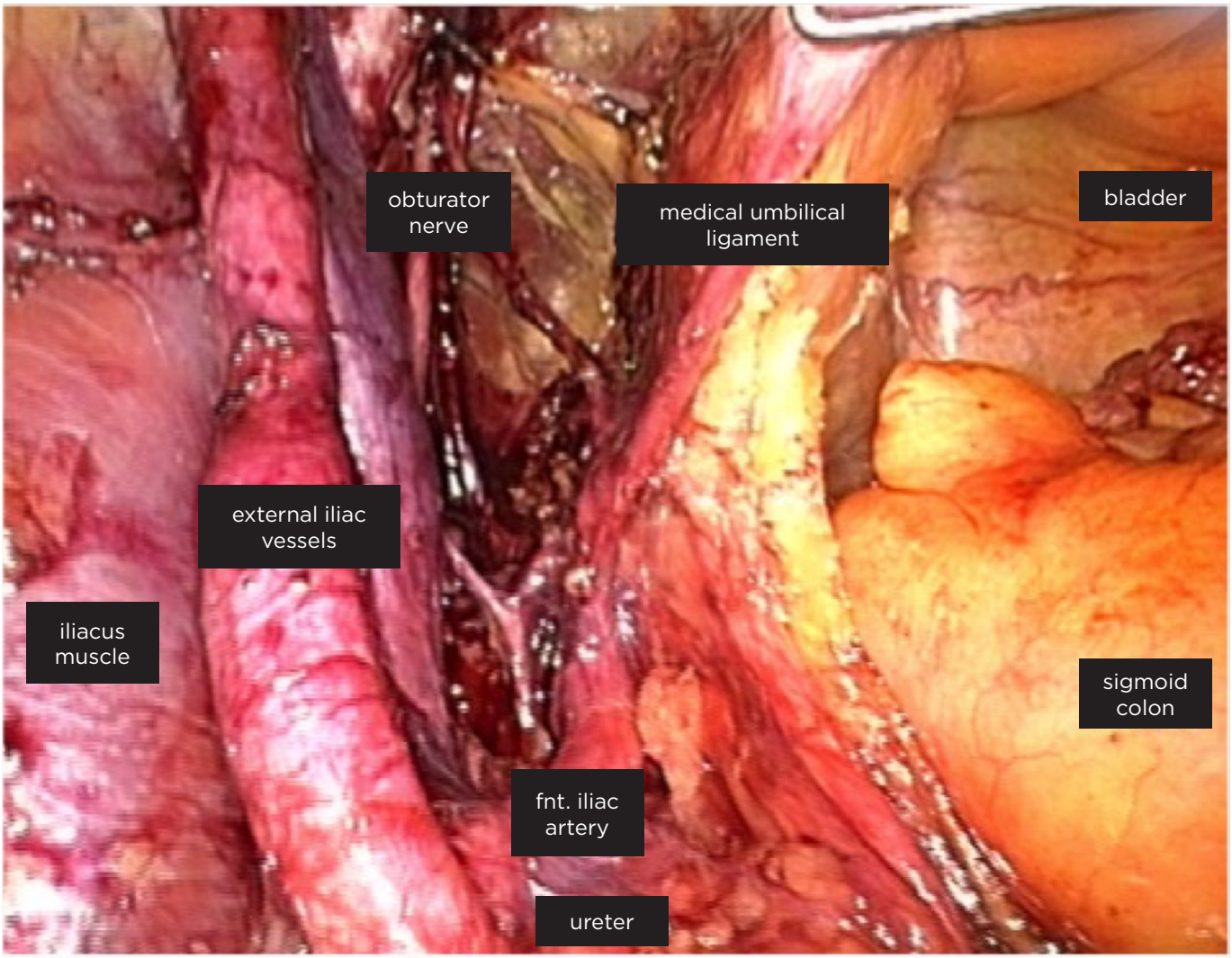


**Figure 1: Extended pelvic lymph node dissection template.**


**Figure 2: Negative surgical margin in pT3a cancer.**

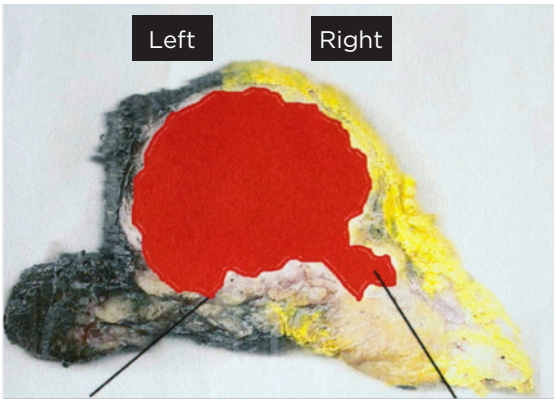


**Figure 3: Negative surgical margin in pT3b cancer.**

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