Leading the way

Dr Alfonso Gomez-Iturriaga explains his research into using new imaging techniques to promote a more complete understanding of prostate tumours and discusses innovative therapies to better treat them.

Could you introduce your research on the use of MRI-TRUS fusion high dose rate (HDR) prostate brachytherapy to target prostate cancer lesions and discuss your overarching objectives?

Prostate brachytherapy is an advanced cancer treatment for localised prostate cancer that offers excellent results in terms of disease control with a safety profile of adverse events. Magnetic resonance imaging (MRI) is nowadays the only imaging technique that provides high soft tissue resolution to assess the local extent of disease within the prostate. Our research is focused on conforming radiation doses delivered by brachytherapy closely to the tumour’s shape and position in order to apply the highest possible dose to the tumour.

What is brachytherapy, and why is it considered the superior technology with regard to dose conformation?

Brachytherapy is a highly targeted cancer treatment in which radiation sources are placed in or near a tumour, giving a high radiation dose to the tumour in a short period of time, while limiting the dose to critical structures, such as the urethra and rectum. Specifically, in prostate cancer, metallic needles or plastic catheters are inserted into the prostate with ultrasound guidance while the patient is under anaesthesia. After the needles are placed, a computer plan will calculate how long the radioactive source will stay in each needle. Since the radiation is delivered directly from the inside of the prostate, the doses are administered with exquisite precision, allowing for higher doses and less adverse events than other radiation techniques. This makes the procedure very safe.

How is HDR brachytherapy administered?

HDR brachytherapy involves the temporary implantation of hollow source-carrier needles (or catheters) in a defined pattern. A highly conformal radiation treatment can then be delivered to the target using a ‘stepping source’ of high activity iridium 192, which is automatically advanced in step-wise fashion, along each of the needles in turn. By varying the ‘dwell times’ at each stopping point, the isodoses can be elegantly contoured to avoid normal structures, cover the target to perfection and even maximise dose delivery to sub-volumes of heavy tumour infiltration within the prostate. The treatment is usually completed in about 15-20 minutes, with a dose rate of about 100 Gy/hr, similar to that of a linear accelerator. The combination of short treatment delivery time, 3D appreciation of the relationship between the anatomy and the needle positions, and dose optimisation to shape isodoses around the urethra and rectum allows precise control over the dose delivery.

New imaging techniques have been developed to improve diagnostic and prognostic accuracy, including MR spectroscopy (MRS), diffusion-weighted MRI (DW-MRI) and dynamic contrast-enhanced MRI. Why is DW-MRI used to evaluate the macroscopic local staging of the disease and more recently, prostate cancer aggressiveness?

Image contrast in DW-MRI is determined by differences in the rates of water molecule movement in biological tissues. In normal prostate tissue, the diffusing capacity is maintained, resulting in low signal intensity on DW-MRI. Prostate cancer tissue has a higher cellular density and the extracellular space decreases. Consequently, in cancer tissue, the water molecule movement is restricted, resulting in high signal intensity relative to surrounding normal tissue on DW-MRI. In addition, differences in water molecule movement are not only quantitatively assessed by the apparent diffusion coefficient (ADC). In fact, some authors have demonstrated a strong correlation of ADC value with the aggressiveness of the prostate cancer measured by the Gleason score, a diagnostic tool medical professionals use to evaluate the prognosis of men with prostate cancer based upon its microscopic appearance.

DW-MRI is able to demonstrate malignant lesions and predict cancer aggressiveness. This information is crucial in order to design appropriate local treatments for prostate cancer.

Why are dominant intraprostatic lesions (DIL) the target of brachytherapy?

Although multifocal tumours are found in roughly 80 per cent of patients, studies of patterns of failure following conventional radiotherapy show that the area responsible for local recurrence is in almost all cases the DIL. In addition, this lesion is presumed to be the main driving factor for the overall behaviour and lethality of the cancer. Consequently, through dose escalation of DIL we should be able to increase disease control.
Combating prostate cancer

A team of Spanish researchers at the University Hospital of Cruces are undertaking groundbreaking research into the impact of MRI technology on diagnosing and treating one of the most common cancers in the world.

PROSTATE CANCER is the second most common cancer in males and the fifth most common cancer worldwide. Since the introduction of screening for the prostate-specific antigen (PSA), the rate of diagnosis has increased significantly and specific mortality has reduced in the majority of Western countries. However, it remains one of the most frequently diagnosed cancers in the developed world and accounts for 12 per cent of newly diagnosed cancer cases in Europe. In Spain, for example, over 25,000 patients per annum are diagnosed with prostate cancer, representing 21 per cent of all tumours in men. Of these, approximately 55 per cent of patients present with intermediate or high-risk of the disease.

Dr Alfonso Gomez-Iturriaga, based at the University Hospital of Cruces in Northern Spain, has pioneered important research into prostate cancer in recent years. His specific interests lie in examining the impact of magnetic resonance imaging (MRI) on the local staging, risk group classification and treatment of prostate cancer in patients undergoing high dose rate (HDR) brachytherapy. Ultimately, his goal is to contribute towards the improvement of both the diagnosis and prognosis of patients with prostate cancer.

MAKING HEADWAY

Traditional methods of evaluating the extent of prostate cancer include rectal examination, transrectal ultrasound (TRUS), sextant biopsies and PSA screening. While each of these techniques is able to differentiate between indolent and aggressive tumours, the fact that most patients present with intermediate tumours means that their accuracy is often limited. In view of these constraints, research has been undertaken to examine the accuracy of MRI in the study of the local extension of prostatic cancer – and results so far have been highly encouraging.

The past decade has seen vast improvements in MRI technology, as well as in the hands-on experience of radiologists using the equipment. New techniques such as MR spectroscopy (MRS), the use of dynamic contrast and diffusion and perfusion techniques have all led to a breakthrough in the ability of MRI to evaluate prostate cancer. This technology is improving constantly and becoming commonplace; indeed, the high-resolution images allow medical professionals to make more detailed assessments about the local extent of the disease. Recent studies have shown an increase in the sensitivity and specificity for the detection of dominant intraprostatic lesions (DIL) when using multiparametric MRI as a diagnostic tool in the staging of the disease.

When analysing the extent of tumour aggressiveness, the MR images and spectroscopy mainly focus on the macroscopic local staging of the disease. This provides important information about the existence of prostate tumour nodules, such as whether they are unilateral or bilateral and – most importantly – whether there is extra-prostatic extension or not, since the presence of extension confers a poor prognosis of the disease. In the same procedure, MRI is also able to detect nodal drainage areas and explore the pelvic bone structures, which in turn rules out nodal or bone metastases.

FAR-REACHING FINDINGS

Brachytherapy companies have recently developed software, called Oncentra® Prostate v.4.0, which allows for TRUS-MR image fusion. Nucletron™ produces the software package as part of Elekta AB, a Swedish company known for providing radiation therapy, radiosurgery and related equipment for treating of cancer and brain disorders, based in Stockholm, Sweden. This software represents a significant step forward because the combination of MR and TRUS is highly useful for both stereotactic prostate biopsy and staging. In their research, Gomez-Iturriaga and his team have found that the fusion of both imaging methods provides important information for prostate brachytherapy, allowing for better coverage and higher doses to extracapsular disease in patients.

In 2011, an important research project was launched at the University Hospital of Cruces that investigated MRI-guided prostate HDR brachytherapy. The researchers selected prostate cancer patients, all of whom underwent a pre-treatment MRI for local staging, followed by combined HDR
brachytherapy and external beam radiotherapy (EBRT). The impact of MRI in the local disease overstaging was found to be striking: while none of the patients were classified as cT3 – that is, as having extra-prostatic disease – by transrectal ultrasound or prostate biopsy, after having the MRI scan, 46 per cent showed the presence of extraglandular extension. This has huge implications for the risk group classification of patients; crucially, when a patient moves from low to intermediate risk, or from intermediate to high risk, this leads to different therapeutic alternatives. In this particular study, the MRI changed the risk group in 56 per cent of cases when using the National Comprehensive Cancer Network classification system and in 24 per cent of cases when using the D’Amico classification system.

Since the study began, the methodology of MRI-TRUS fusion has evolved rapidly: “Initially the brachytherapy was performed using what is called cognitive fusion,” Gomez-Iturriaga discloses. “This involved an estimation of the location of the lesion on the part of the TRUS operator. It varies greatly with expertise, so we soon commenced work on the real-time MRI-TRUS fusion.”

The first patients in the study were treated with the standard technique of HDR brachytherapy, combined with external beam radiotherapy.

The success of this procedure soon became apparent, leading to the development of two novel treatment techniques. The first involves administering the whole dose in a single fraction of HDR brachytherapy for patients with low to intermediate risk prostate cancer; this only takes two hours and allows the procedure to be performed on an outpatient basis. The second procedure involves administering a dose that is 25 per cent higher than the prescribed amount to the DIL, as defined on the multi-parametric MRI, for both intermediate and high-risk prostate cancers. In this particular case, the patients also receive a short course of external beam radiotherapy.

DOSE ESCALATION

The purpose of Gomez-Iturriaga’s most recent study is to demonstrate the feasibility of delivering a higher-than-prescription brachytherapy dose to the dominant intra-prostatic nodule as defined on multiparametric MRI. The preliminary results of the study – which began in May 2013 – have not yet been published but were presented at the UK Prostate Conference in Dublin in March 2014.

The study confirms that among the various irradiation techniques currently used for prostate cancer, brachytherapy is superior in terms of its dose conformity. It allows greater dose escalation and adjusting of the isodoses to the prostate with high accuracy, while keeping healthy adjacent organs – such as the urethra and rectum – in a tolerable dose range: “Our initial findings demonstrate that dose escalation to the DIL to a mean of 125 per cent of the prescribed dose for selected intermediate and high-risk prostate cancer patients is feasible, while respecting critical organ constraints,” Gomez-Iturriaga states. “The precise control over dose delivery inherent in HDR brachytherapy is not readily achievable with other radiation techniques.”

NEXT STEPS

There is currently very little research being conducted into the role of pre-treatment MRI-TRUS image fusion and HDR brachytherapy for prostate disease. If the findings of Gomez-Iturriaga’s study prove successful, this will have ramifications for treatment, opening doors for more focused treatments without side-effects.

Looking ahead, Gomez-Iturriaga foresees that his team’s next steps will involve designing a focal therapy trial that avoids treatment to unnecessary regions of the prostate. Focal therapy is a damage-limitation approach, carefully selecting the tumours within the prostate gland with the use of multi-parametric MRI and targeting them with highly focused HDR brachytherapy. Fundamental for reducing the potentially harmful effects of radiotherapy to healthy tissue, this approach heralds superior and enhanced treatment for patients with prostatic disease.