

Prostate Cancer : New Advances in Imaging and Radiation Treatment

Metro North Hospital and Health Service *Putting people first*



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RBWH



Prostate Cancer : New Advances in Imaging and Radiation Treatment



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Newer Imaging technologies that assist in clinical staging ,monitoring and radiotherapy treatment planning

- * Prostate cancer detection based on digital rectal examination (DRE) and prostate-specific antigen (PSA) level testing in blood**
 - * DRE crude tool ; low predictive value**
 - * PSA is highly sensitive but not specific for prostate cancer. Benign pathologies such as benign prostatic hyperplasia can raise PSA levels and normal PSA levels can not exclude prostate cancer.**
- * Prostate biopsies are assessed histologically by the Gleason score, a prognostic factor of prostate cancer, which provides information on tumour aggressiveness- failure of detection in 25% cases**
 - * TRUS biopsy needles reach only the posterior 15mm of the prostate avoid, aim to avoid bladder neck, apex or both; collectively only sample 1% of gland.**

Newer Imaging technologies that assist in clinical staging, monitoring and radiotherapy treatment planning

- * Aim to divide prostate cancer into being clinically significant or insignificant depending on its likelihood to affect a patient's lifetime.
 - * No universal definition for clinical significant prostate cancer.
 - * Most frequent applied definition: Pathology/histology with Gleason score ≥ 7 (including 3 + 4 with prominent but not predominant Gleason 4 component), and/or volume ≥ 0.5 cc, and/or extra prostatic extension (EPE) .
 - * Depending on Gleason score and clinical assessment of the patient's disease, treatment options for prostate cancer are active surveillance, surgery and radiotherapy.
- * Problem : Current conventional strategies employed to stage and delineate prostate cancer include DRE, PSA level ,random biopsies of prostate ,CT abdomen and pelvis and bone scan underestimate location and extent of disease in 20-30% cases
 - * High grade occult disease ,
 - * EPE when it is located in lateral peripheral zone, anterior gland, superior base or inferior apex .
 - * CT rarely helpful unless gross EPE or SVI

Newer Imaging technologies that assist in clinical staging, monitoring and radiotherapy treatment planning

Multiparametric MRI (mp MRI) of prostate- imaging modality of choice for detection of localised prostate cancer.

Part of standard of care for diagnosis, clinical staging, monitoring and treatment planning and in conjunction with PSMA PET may assist in reducing some of the uncertainties of clinical staging , monitoring and treatment planning.

Negative Mp MRI proposed as an exclusion criteria for repeat biopsy and positive Mp MRI can be a trigger for repeating biopsies- may prevent repeated biopsies

MRI : Anatomical MRI T2W/T1W- images to discriminate between anatomical zones of the prostate and differentiate normal tissue from abnormalities .

Benign conditions such as BPH or prostatitis may mimic T2W appearance of prostate cancer and intra-prostatic cancerous tissue may not be detected.

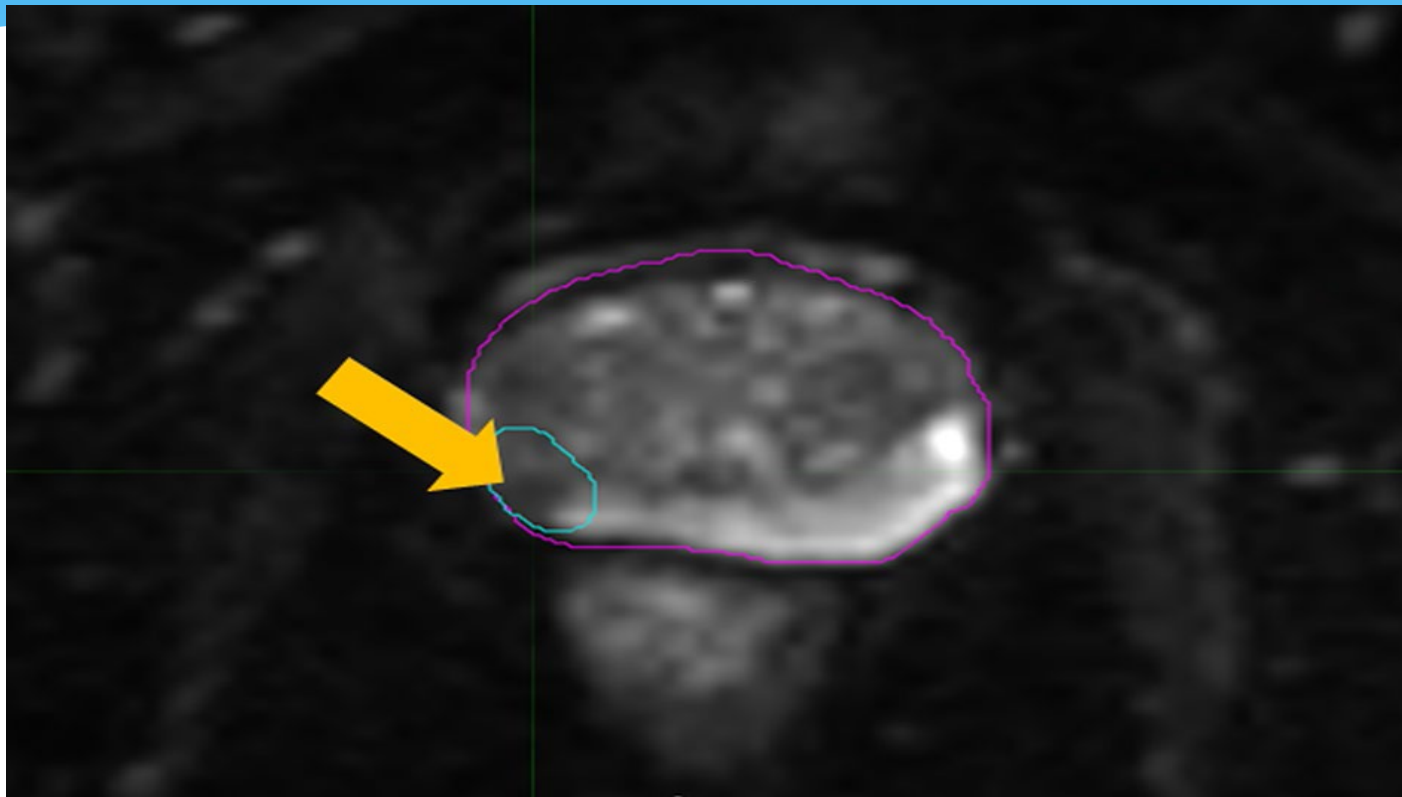
Newer Imaging technologies that assist in clinical staging, monitoring and radiotherapy treatment planning

Multiparametric MRI :

Includes 2 functional sequences in addition to T2 and T1 weighted imaging

- **Diffusion weighted images (DWI)- functional method of measuring water molecule diffusion rates within tissue . Prostate cancer present with restricted diffusion rates relative to normal prostate tissue – (looks bright on DWI)**
- **Changes in DWI represented through diffusion coefficient (ADC) maps computed at each image voxel- abnormalities appear hypointense on ADC maps**
- **T2w and DWI detect prostate cancer in 92% cases**

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Diffusion-weighted imaging (DWI) of an axial midland plane with high b value ADC map. Areas of higher water diffusion rates appear brighter on T2 imaging. Significant cancers may present with restricted diffusion rates and are seen as areas of hypointense signal on the ADC map (arrow). The focal lesion is contoured for clarity

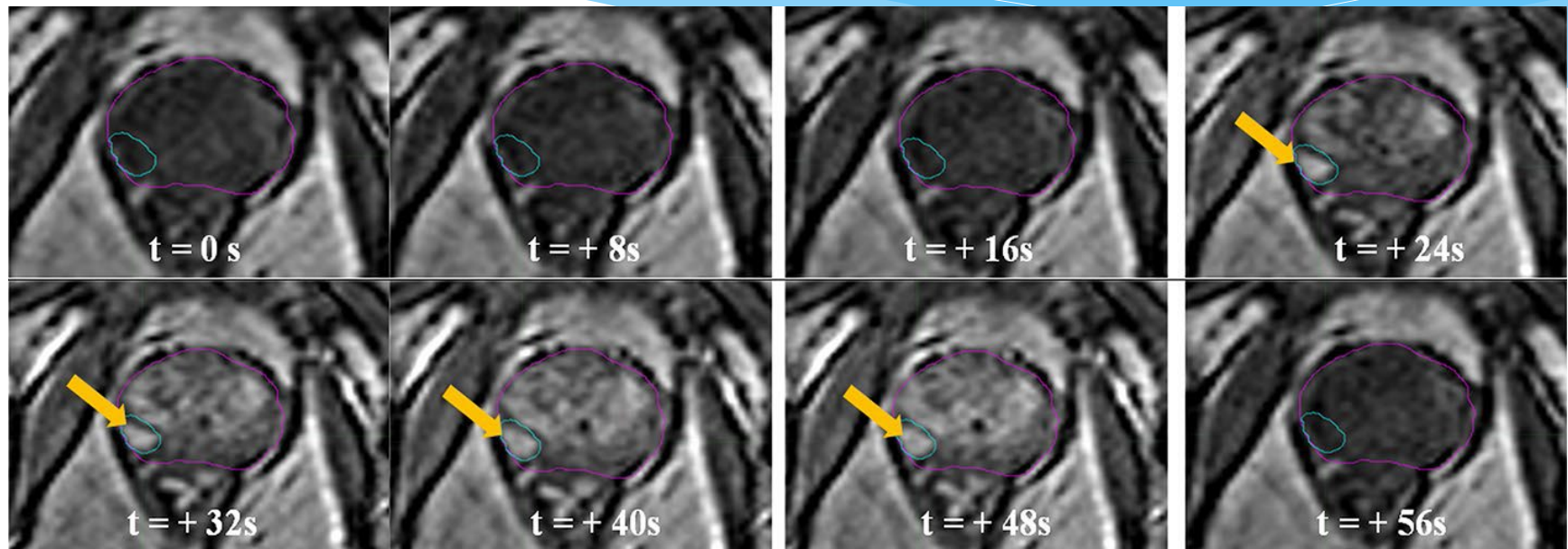
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Multiparametric MRI :

Includes 2 functional sequences in addition to T2 weighted imaging

- **Dynamic contrast –enhanced images (DCEI) obtained by acquiring T1W image sequences during administration of gadolinium based contrast agent. Takes advantage of cancer angiogenesis with increased vascular density and permeability within tumours to show prostatic regions of increased uptake of gadolinium**

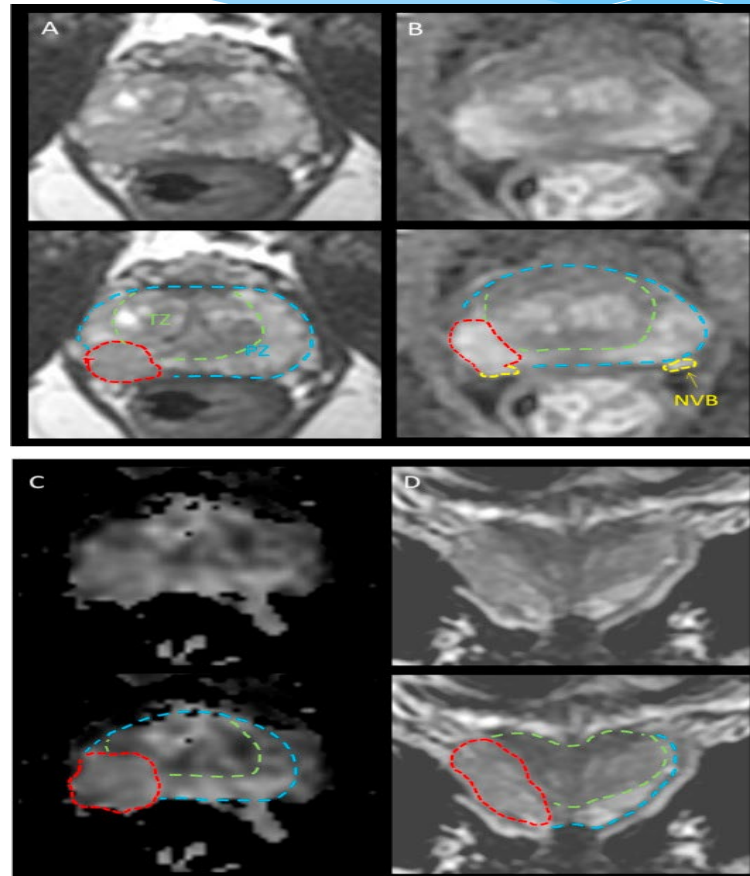
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Axial midgland sequence showing dynamic contrast-enhanced imaging (DCEI) acquired using T1W-FSE sequences over a 1 min period. Gadolinium-based contrast agent (GBCA) is administered intravenously at an injection rate of 2–3 cc per second; lesion enhancement may appear as early as 10 s following injection. Enhancement of the DIL is shown in frames 4 through 7 (arrows), followed by a washout phase where the signal dissipates

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mpMRI in a 63-year-old with PSA 6.5, Gleason 3 + 4 in 3 of 6 biopsies on right, 3 + 3 = 6 in 2 of 6 biopsies on left. DRE stage = cT2b (right lobe). (A) T2 demonstrates a right-sided lesion with probably ECE, (B) DCE demonstrates enhancement with probable ECE and probable extension to the NVB on right, (C) DWI demonstrates definite ECE, and (D) coronal T2 view demonstrates extension throughout the lobe with effacement of the boundary consistent with ECE, though no SVI. T, tumor; PZ, peripheral zone; TZ, transition zone; NVB, neurovascular bundle.



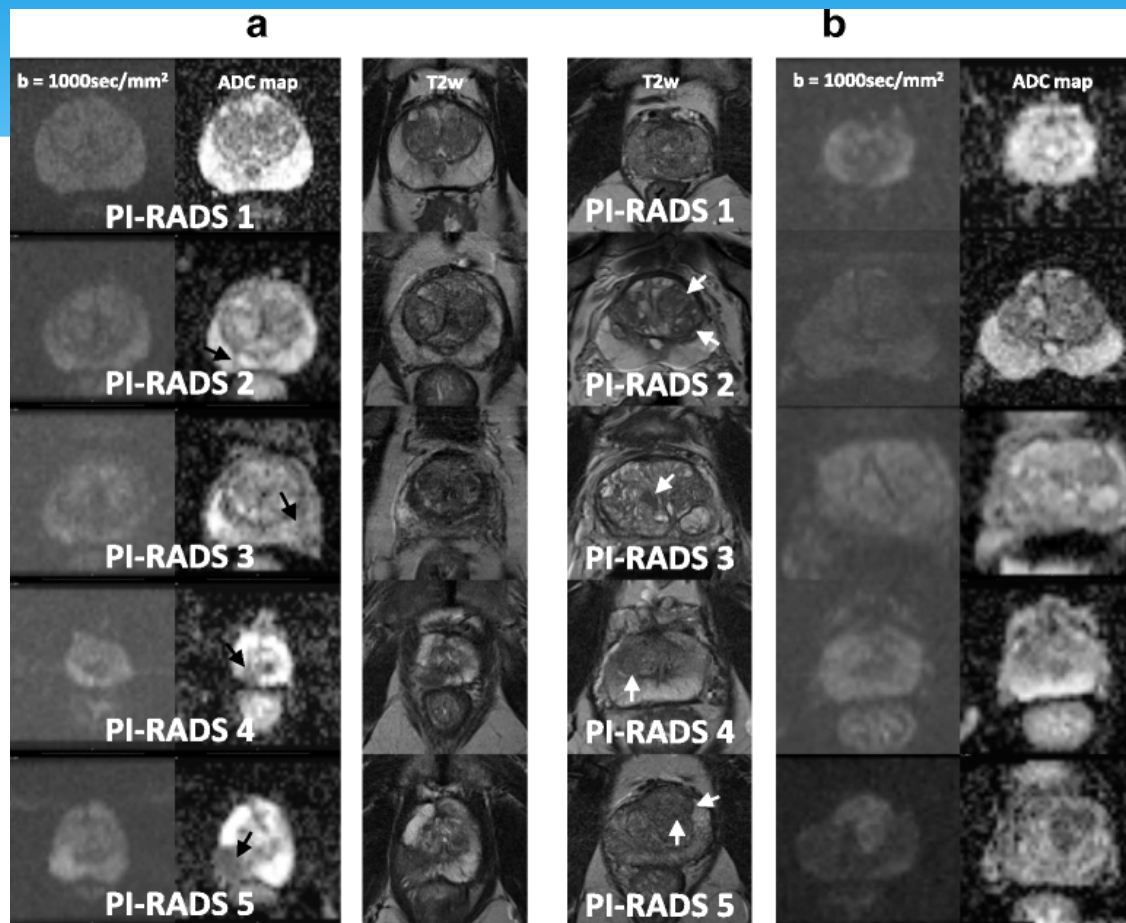
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- * Inclusion of DWI and DCEI improved sensitivity and lesion detection of prostate cancer particularly in peripheral zone. Also provide insight into biological activity of intra-prostatic lesions not appreciated with T2 W sequences.**
- * 3 sequences are combined after radiographic characteristics from each sequence are scored and categorised using the prostate imaging – reporting and data system (PI-RADS) which relies on 5 point scale and developed to standardise approach to diagnosis and reporting of prostate cancer.**
- * PI-RADS system correlates with predict Gleason score and assists in identifying clinically significant cancer.**

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- * **PI-RADS System v2 : “Prostate Imaging Reporting and Data System” (PI-RADS) is published by the European Society of Urogenital Radiology (ESUR) and was initially adapted from breast imaging**
- * **The latest PI-RADS version assesses the likelihood (probability) of clinically significant prostate cancer on a 5-point scale for each lesion as follows:**
- * **PI-RADS 1 – Very low (clinically significant cancer is highly unlikely to be present)**
- * **PI-RADS 2 – Low (clinically significant cancer is unlikely to be present)**
- * **PI-RADS 3 – Intermediate (the presence of clinically significant cancer is equivocal)**
- * **PI-RADS 4 – High (clinically significant cancer is likely to be present)**
- * **PI-RADS 5 – Very high (clinically significant cancer is highly likely to be present)**

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Peripheral zone shows PI-RADS assessment categories with DWI as dominant sequence. 1. No abnormality (i.e. normal) on the high b-value DW image and on the corresponding ADC map as well as on the T2w image. 2. Isointense signal of the peripheral zone on the high b-value DW image with an indistinct linear hypointense lesion on the ADC map (arrow) with corresponding T2w hypointense signal. 3. Isointense/mildly hyperintense signal of the peripheral zone on the high b-value DW image and with a focal mildly/moderately hypointense indistinct lesion on the ADC map (arrow). T2w image shows heterogeneous signal intensity of the peripheral zone. 4. Focal markedly hyperintense lesion on high b-value DW image with corresponding markedly hypointense signal intensity on the ADC map (arrow). Lesion size is < 1.5 cm on axial images. T2w image shows a circumscribed homogenous hypointense lesion. 5. Same as 4, but lesion size is ≥ 1.5 cm in greatest dimension (arrow). Definite extraprostatic extension/invasive behaviour (not shown) would also qualify for this category.

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Advantages of MP MRI:

1. Stage and grade newly diagnosed disease:

- **EPE** :presence can influence type of therapy used, determine margins for radiotherapy.
- **Gleason grade** : use of ADC maps of DWIs to identify occult high grade disease:

Once occult disease detected targeted biopsies can be performed transrectally, transperineally, or even by a transgluteal approach. This information important when discussing active surveillance or monitoring patients on active surveillance.

- **SVI** :often undetected with current strategies – carries significant clinical consequences on prognosis and treatment planning for EBRT and brachytherapy

Newer Imaging technologies that assist in clinical staging, monitoring and radiotherapy treatment planning

Advantages of MP MRI:

2. Influence management of prostate cancer

- utilised for active surveillance- suitability and ongoing monitoring
 - ?reduce need for multiple surveillance biopsies
- Assist in locating residual disease after failure of prostatectomy.
- Enable selection of local therapy – intermediate risk patients treated with definitive brachytherapy- add EBRT if EPE or SVI detected .
- Enable intensification of local therapy - boosting the dominant intraprostatic lesion with brachytherapy or EBRT
- Improve the quality of treatment planning- better determination of location of disease, anatomy of gland and critical organ structures such as neurovascular bundle with prospect of decreasing acute and late effects.

Newer Imaging technologies that assist in clinical staging, monitoring and radiotherapy treatment planning

Positron Emission Tomography (PET)

PET is a molecular imaging modality which uses tracers to bind malignant cells

Multiple PET tracers used to evaluate location, burden and activity of prostate cancer including ^{18}F -flurodeoxyglucose PET, choline labelled PET(^{18}F -choline and ^{11}C - choline) and PSMA PET.

Despite significant advances in use of choline and flurodeoxyglucose tracers , their diagnostic capability is limited

Cannot reliably identify local recurrence, lymph node involvement or soft tissue deposits.

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PSMA PET (Prostate specific membrane antigen)

Prostate specific membrane antigen is a transmembrane glycoprotein with an extracellular portion located in the epithelium surrounding the prostatic ducts. PSMA is also expressed in other tissues such as the kidney, proximal SI and salivary glands.

Dysplastic changes in prostate result in expression of PSMA on luminal surface of prostatic ducts.

Expression in prostate cancer cells 100-1000 fold that of normal cells and over expression increases with tumour grade, androgen independence and stage of disease including metastatic and disease recurrence.

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- **PSMA is an ideal target for imaging of prostate cancer and therapy**
 - **Mainly expressed in prostate cancer of all stages of disease**
 - **Upregulated in androgen independent or metastatic disease**
 - **Expressed on cell surface**
 - **Not released into circulation**
 - **Internalised after antibody binding.**
- **Several antibodies used to target PSMA. Most effective has been a small molecule inhibitor radiolabelled with ^{68}Ga (gallium 68) that binds with high affinity to the PSMA receptor.**

Newer Imaging technologies that assist in clinical staging, monitoring and radiotherapy treatment planning

⁶⁸Ga PSMA PET

- **⁶⁸Ga long shelf life and is cost effective.**
- **Provides sufficient levels of radioactivity for high quality images, short scanning time while minimising dose to patient and personnel.**
- **Evidence suggests it is safe.**

⁶⁸Ga-PSMA is more effective in detecting metastases, lymph nodes and recurrent prostate cancer when compared with choline based and FDG PET and CT scans

The imaging is effective in patients with low PSA levels and is positively correlated with rising PSA levels and tumour size but is negatively correlated with PSA doubling time.

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Staging:

- Majority of studies evaluating role of ⁶⁸ Ga-PSMA PET include patient with intermediate or high risk disease
- CT/MRI staging of regional nodes – relies on change in LN morphology and size criteria however 80 % of metastatic involved nodes < 8mm size used in clinical practice.
- For detection of involved nodes :CT/MRI –sensitivity of 39-42% and specificity of 82% .
:Choline based PET tracers-sensitivity of 49.2% and specificity 95% .
: ⁶⁸ Ga PSMA PET - sensitivity 65.9% and specificity of 98.9% ⁱ

Newer Imaging technologies that assist in clinical staging, monitoring and radiotherapy treatment planning

Secondary staging following biochemical recurrence:

- Several studies now suggest that ⁶⁸ Ga-PSMA provides superior diagnostic information compared with CT, MRI and choline based PET. ²³
- Is valuable in cancer that exhibit low PSA values
- Perera et al metanalysis of sensitivity, specificity and predictors of positive Ga PSMA PET ⁴showed better sensitivity for ⁶⁸ Ga PSMA PET in detecting recurrence at low PSA levels or short PSA doubling times than choline-based PET.
- ⁶⁸ Ga PSMA PET positive in 42% with PSA 0- <0.2ng/ml ,
58% for PSA 0.2-0.99,
76% for PSA 1-1.99

² Bleumal C et al Clin Nucl Med 2016;41:pp515-521.

³Pfister D. et al, Eur J Nucl Med Mol Imaging 2016;43: pp1410-1417.

⁴Perera et al .,Eur Urol 2016;70pp926-937.

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- Summary of detection rates of ⁶⁸Ga-prostate-specific membrane antigen for different prostate-specific antigen levels

Study	Detection rates (%)			
	≥2 ng/mL	1<2 ng/mL	0.5<1 ng/mL	0.2<0.5 ng/mL
Eiber <i>et al.</i>	96.8	93	72.7	57.9
Verburg <i>et al.</i>	89	79		44
Bluemel <i>et al.</i>	71.4	45.4		28.6

- 64% for PSA doubling time < 6months⁴

² Bleumal C et al Clin Nucl Med 2016;41:pp515-521

⁴Perera et al ., Eur Urol 2016; 70; pp926-937

⁵ Eiber et al.,

⁶ Verberg et al.,

Emerging technologies in Radiation Therapy for Prostate Cancer

- * Past 10 yrs able to precisely target and deliver radiotherapy to spare normal tissues surrounding prostate from excess radiotherapy and toxicity.
- * Multiple randomised trials of EBRT +/- brachytherapy boost, including a meta-analysis have shown improved BRFs when treatment doses escalated beyond 70Gy⁶⁷⁸⁹ Most benefits are seen in patients with intermediate and high risk disease. Dose escalation with EBRT results in increased rectal toxicity. Current treatment regime: 78Gy -81Gy in 39#
- * Technologies such as stereotactic body radiotherapy, proton beam radiation and high dose rate brachytherapy deliver highly conformal treatment, with the prospect of dose escalation while reducing toxicity to adjacent normal tissues.
- * Classical radiobiology suggests that prostate cancer is sensitive to large doses of XRT per treatment – rationale for moderate Hypofractionated IMRT, SBRT and High Dose Rate Brachytherapy.

Emerging technologies in Radiation Therapy for Prostate Cancer

SBRT or Stereotactic Ablative Radiotherapy – form of XRT in which smaller number of fractions (≤ 5), each of comparatively high dose to the volume using highly conformal techniques to minimise dose to tissues adjacent to the prostate.

Used as Monotherapy or Boost following EBRT

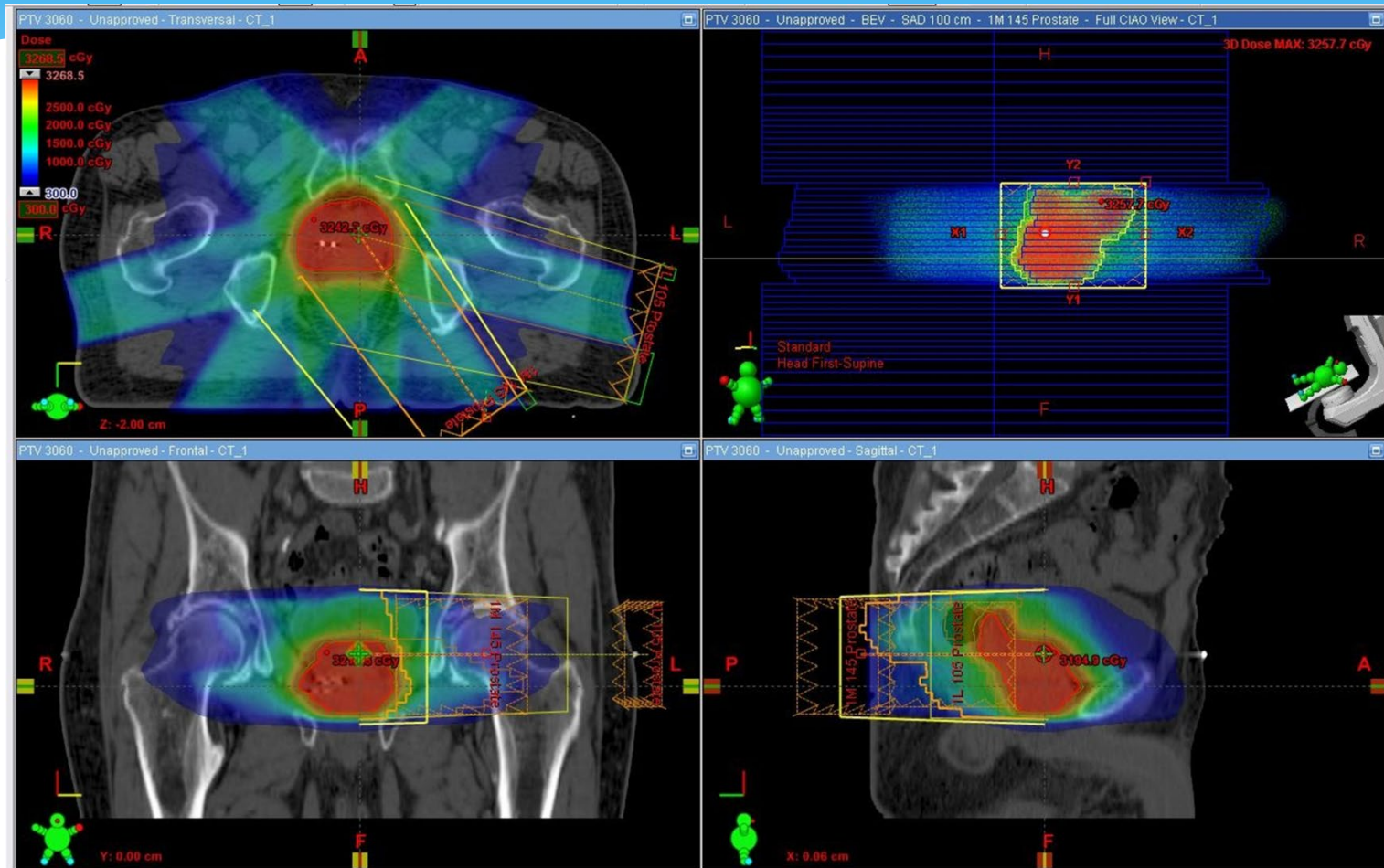
- * **Many single institution studies utilising SBRT have been performed treating patients with low –intermediate prostate cancer delivering doses of 35.0 Gy - 40 Gy in 4-5# . (Compare with 78Gy in 39#)**

King et al reported 1100 patients in multiple prospective clinical trials. 58% low risk disease, 30% Intermediate risk and 11% high risk disease. Median followup : 36 months

Results: 5yr BRFS 95%, 84% and 81% respectively. ⁹

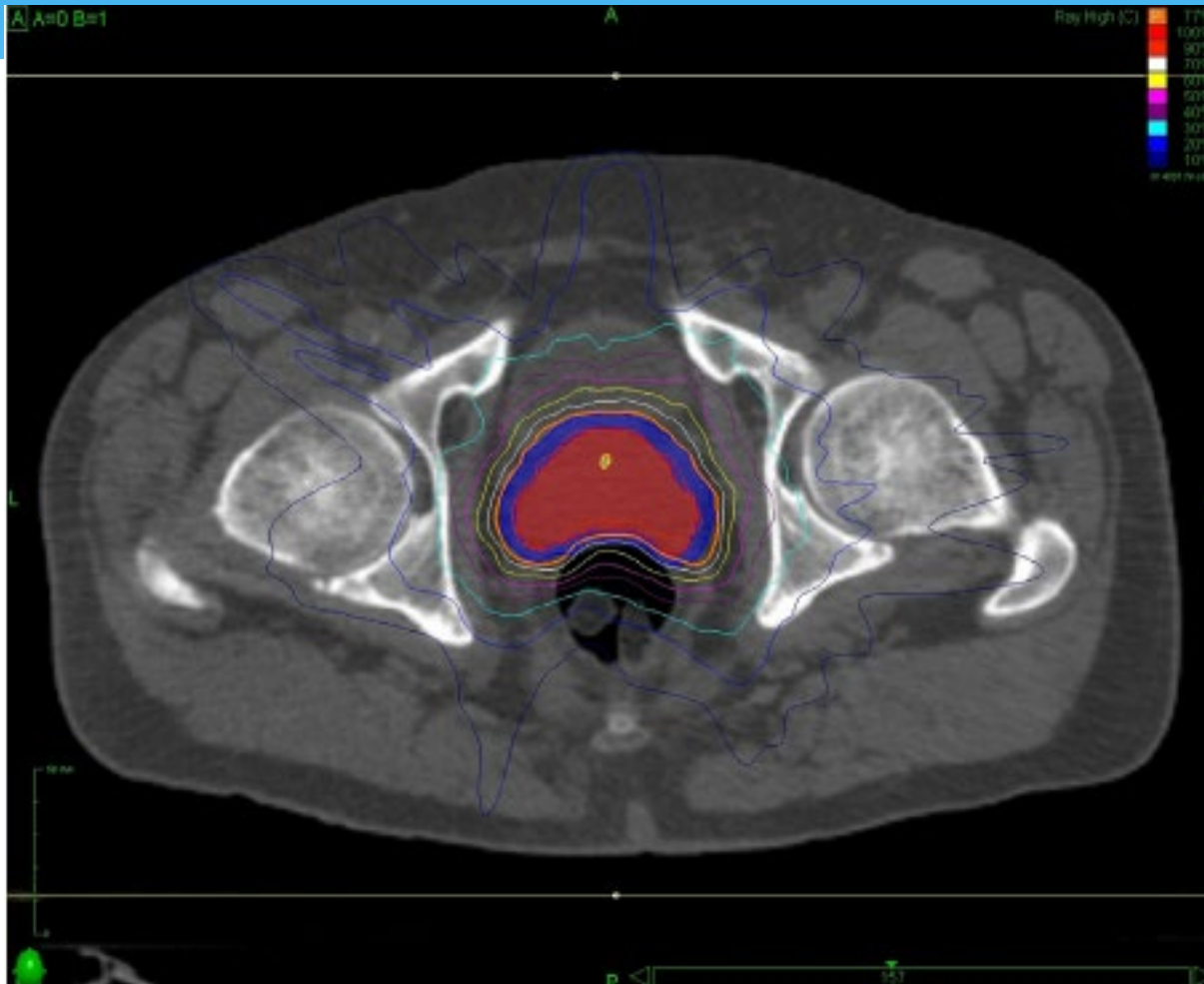
- * **Several ongoing randomised trials comparing SABR with conventional fractionated IMRT –no results as yet**
- * **Efficacy comparisons utilizing BRFS suggest SABR compares favourably with patients receiving fractionated IMRT or brachytherapy monotherapy using HDR or LDR in low and intermediate risk disease.**

Emerging technologies in Radiation Therapy for Prostate Cancer



IMRT plan for prostate cancer

Emerging technologies in Radiation Therapy for Prostate Cancer



SABR plan prostate cancer

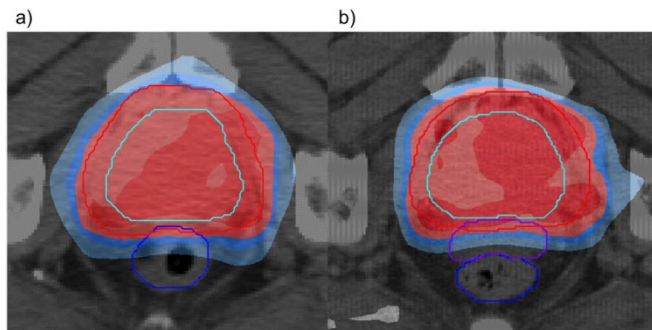
Emerging technologies in Radiation Therapy for Prostate Cancer

Use of SBRT monotherapy for high risk patients more controversial- SBRT investigated as a means of delivering a boost to prostate after pelvic regional radiotherapy. Reported outcomes have been favourable and toxicity acceptable

SABR also being investigated as a boost for dominant intraprostatic lesions.

Safety : prostate localisation techniques – continuous tracking of implanted fiducial markers or use of an absorbable injectable hydrogel spacer that is implanted into the recto-prostatic space.

Recent randomised trial assessing safety and efficacy of the spacer : 99% placement success rate ; significant reduction in late rectal toxicity and significantly reduces rectal dose in prostate SABR plans.



Dose distribution a) pre and b) post injection of spacer gel

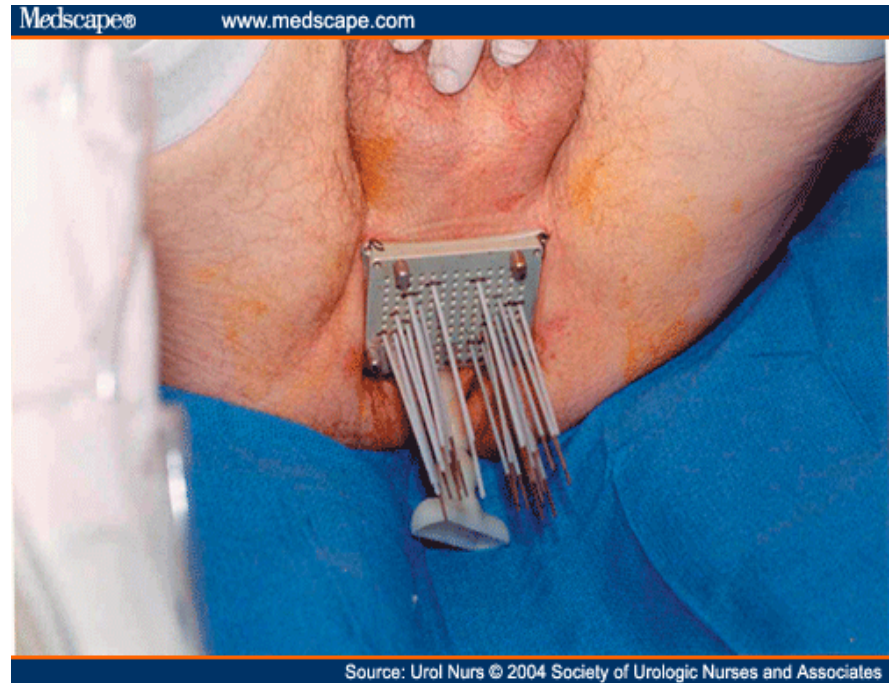
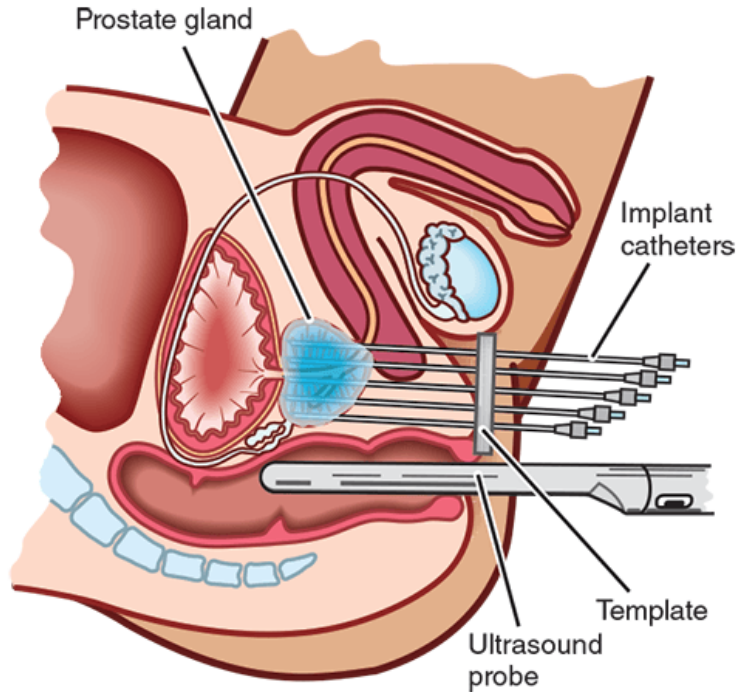
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HDR Brachytherapy:

Allows for a degree of conformality and dose escalation that is difficult to achieve with EBRT

- Temporary implant unlike I131 LDR seed therapy which is permanent
- Delivers radiotherapy at a dose $> 12\text{Gy}/\text{Hr}$ using Ir 192 as most commonly used isotope.
- Treatments performed as outpatient if single fraction or as inpatient when multifraction
- Procedure performed under GA or epidural and conscious sedation using TRUS guidance for needle placement.
- Template sutured to perineum and stabilising needles inserted and catheters placed
- Once catheters in place , CT, TRUS or MRI obtained to ensure proper placement and treatment planning purposes.

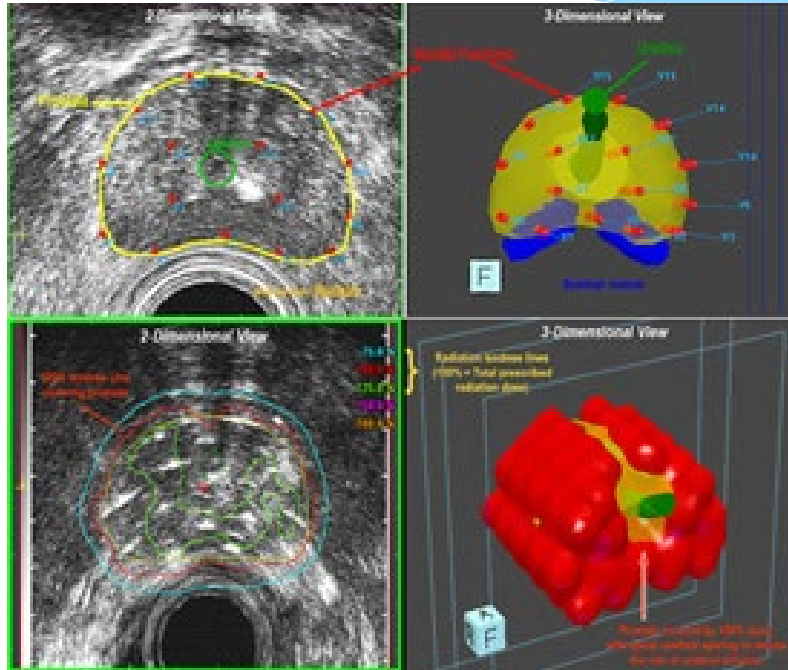
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Template and HDR needles in situ

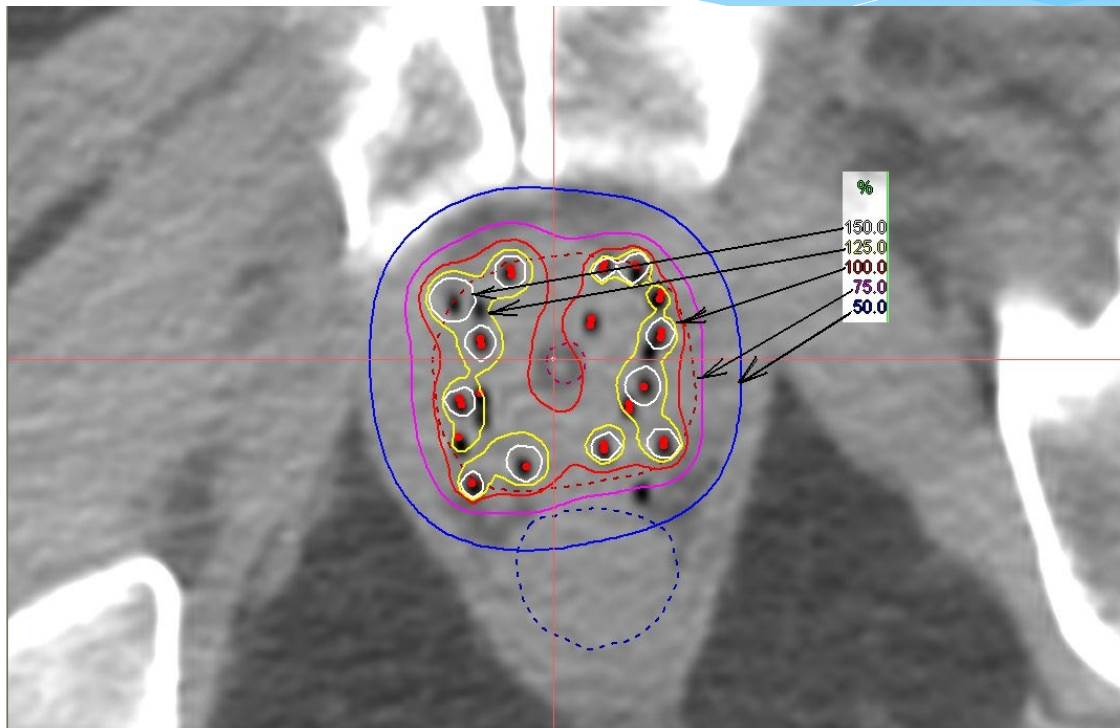
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TRUS image with prostate contoured



Online US planning and dose distribution

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Dosimetry for HDR brachytherapy

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HDR brachytherapy

- Used as a boost following EBRT to dose escalate to treat patients with high risk and intermediate risk prostate cancer.
- Used as monotherapy in patients with intermediate and high risk prostate cancer

Boost

- most of early series delivered multiple fractions with one or more implants. RBWH : 3 # x 6.5GY delivered over 2 days.
- More recently trend towards fewer fractions and single implants of 15Gy for patient convenience.
- Results have been favourable

HDR brachytherapy BOOST

- **Limited randomised trials comparing EBRT +/- brachytherapy boost**
- **Studies shown significant improvement in BRFs but no OS benefit**
- **Toxicity profiles favourable: urethral stricture -10%, urinary incontinence <1% (higher if previous TURP), severe late rectal toxicity -0%, erectile dysfunction 77%**
- **HDR focal boosting of MRI detected dominant intraprostatic lesions shown to be feasible and currently being investigated**

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Emerging technologies in Radiation Therapy for Prostate Cancer

HDR brachytherapy Monotherapy

More commonly trialled in patients with Intermediate risk prostate cancer
Concerns about adequate coverage of EPE in high risk patients.

Zamboglou et al series of 718 patients (55% low risk, 25% intermediate risk, and 20% high risk) treated with TRUS guided HDR monotherapy using 4x 9.5 Gy (2 implants) or 11.5 Gy x3# (3 implants); ADT used in 56% patients ;

Results: 8 YR BDFS : 82% in high risk patients

Toxicity: Late Gde 3 GU and GI toxicity :3.5% and 1.6%

:81% retained erectile function suitable for intercourse.

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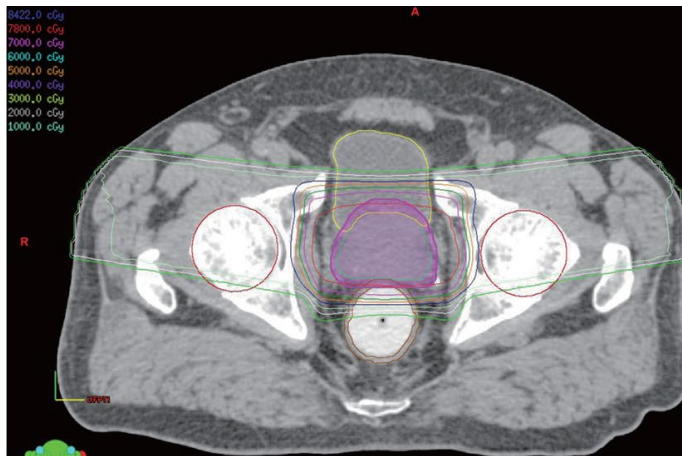
Advantages of HDR Brachytherapy:

- Delivers high dose per treatment – radiobiologically advantageous
- HDR plans are optimised and delivered with catheters in place
- No need to account for movement of prostate.
- Conformality of dose can be optimised and dose to surrounding normal tissues significantly minimised compared with IMRT dose delivery.
- Contraindications: prior TURP, significant urinary symptoms (IPSS>20)
- * Cautions: large prostatic volume(>50cc)in relation to pubic arch, inflammatory bowel disease, non rheumatoid collagen vascular disorders, previous pelvic XRT.

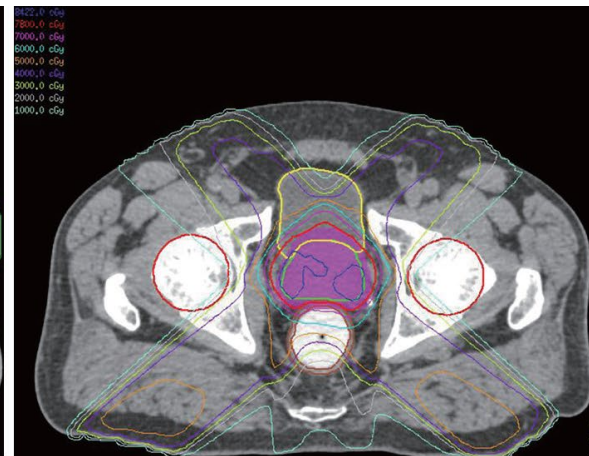
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Protons:

- * Charged particles travel a finite distance, proportional to their speed which can be controlled during acceleration process.
- * Deposit most of their energy at the end of their range (“Bragg Peak”) and there is no exit dose beyond the target
- * Entrance dose also low compared with other forms EBRT



Proton dose plan



IMRT dose plan

Emerging technologies in Radiation Therapy for Prostate Cancer

Advantages:

- * Potential to reduce excess XRT to surrounding organs
- * Reduced number of beams to treat target
- * ? May reduce second malignancy rate in survivors >10yrs
 - * (lower scattered and integral dose)

Emerging technologies in Radiation Therapy for Prostate Cancer

Disadvantages:

- * Cost –more expensive than any other radiation therapy techniques
- * Watch this space!

Prostate Cancer : New Advances in Imaging and Radiation Treatment

Metro North Hospital and Health Service *Putting people first*



Thank-You!



Newer Imaging technologies that assist in clinical staging, monitoring and radiotherapy treatment planning

Lymphotropic Nanoparticle- Enhanced MRI

Uses lymphotropic magnetic nanoparticles to assess lymph nodes

- **50 % patients with high risk disease have pelvic lymph node involvement.**
- **CT /MRI rely on size criteria for nodal characterisation –sensitivity of 30%**
- **Nodal staging with LN-MRI demonstrated 94-96% sensitivity and similar specificity independent of nodal size**