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Potential for focal magnetic resonance-guided stereotactic body radiotherapy for prostate cancer: A review

Abstract

Prostate cancer is the most commonly diagnosed cancer among Australian men. Current whole gland radiotherapy treatment regimens are associated with known toxicities. The MR-Linac has the capability to deliver real-time visually guided radiation to enable focal therapy and reduce toxicity through decreasing radiation doses to organs at risk. This review article discusses the rationale, potential benefits and limitations of the MR-Linac in focal prostate stereotactic body radiotherapy (SBRT), in an effort to reduce toxicity-related side effects for men with low to favourable-intermediate risk prostate cancer. Pubmed was systemically for all published and ongoing trials using the search terms 'Prostate' and 'MRI Linac or MR Linac'. 8 articles were reviewed, of those 1 was deemed relevant, additions were made and expert opinions in the field were sought regarding the most relevant research.

Real-time MRI imaging during the delivery of each fraction with daily plan adaption is now a reality due to the development of the MR-Linac system. It is hoped that with improved real-time imaging, treatment accuracy can be improved, increasing the percentage of the planning target volume receiving the prescribed dose while reducing radiation to the surrounding organs at risk. Early results of prostate SBRT are promising but further research is needed into long term survival benefits and toxicity related outcomes. Focal stereotactic radiotherapy for low-risk intermediate prostate cancer using the MR-Linac has the potential to provide adequate tumour control while decreasing the toxicity and quality of life impact of whole gland treatment for men with localised prostate cancer.

Keywords: prostate cancer, radiation oncology, MR-Linac, radiation toxicity

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Abbreviations: ART, adaptive radiation therapy; CBCT, cone beam computed tomography; CTV, clinical target volume; DCE, diffusion contrast enhanced; DWI, diffusion Weighted Image; EPIC, expanded prostate cancer index composite; GI, Gastrointestinal; GU, Genitourinary; IIEF, international index of erectile function; IMRT, intensity modulated radiotherapy; mp, multiparametric; MRI, magnetic resonance imaging; MR-Linac, magnetic resonance imaging linear accelerator; OAR, organs at risk; PTV, planned treatment volume; PSMA PET, prostate specific membrane antigen positron emission tomography; SABR, Stereotactic ablative radiotherapy; SBRT, stereotactic body radiotherapy

Introduction

Prostate cancer is the most commonly diagnosed cancer and second most common cause of cancer-related death among Australian men.[1] It was estimated that 3152 Australian men died from prostate cancer in 2020.[2] One in 6 men will be diagnosed with prostate cancer by the age of 85, with over 63% of cases diagnosed among men over 65 years.[3] Patients with prostate cancer have a 5-year survival approaching 100% if detected in early stages with a low Gleason Grade. This decreases to 36% when diagnosed at stage 4.[1]

Current whole gland radiotherapy treatments for prostate cancer can be associated with bowel, bladder, sexual side effects and reduced quality of life. It is anticipated that the magnetic resonance imaging linear accelerator (MR-Linac), a magnetic resonance imaging (MRI) scanner incorporated into a radiation linear accelerator, will enable focal therapy to be delivered to the prostate with greater precision. This would lead to reduced radiation doses to surrounding organs, resulting in reduced toxicity and improved quality of life. The aims of this article are to analyse new and existing radiological treatments to the prostate gland, and discuss the potential benefits of the MR-Linac. Pubmed was systemically searched for all published and ongoing trials using the search terms 'Prostate' and 'MRI Linac or MR Linac'. 8 articles were reviewed, of those 1 was deemed relevant, additions were made and expert opinions in the field were sought regarding the most relevant research.

External beam radiotherapy for prostate cancer

Traditionally, definitive radiation therapy for prostate cancer is planned and delivered with x-ray (kV) or cone beam CT (CBCT) guidance. Other technologies such as ultrasound are used much less frequently. The target includes the entire prostate gland and in Australia, 78 Gy delivered in 39 fractions over 8 weeks is the most common dose fractionation. Whole gland radiation of the prostate comes with a risk of gastrointestinal, genitourinary and sexual side effects. Toxicities range from urinary frequency, nocturia, incontinence and haematuria, to rectal bleeding, diarrhoea and abdominal pain, erectile dysfunction and haematospermia. Recent studies have suggested that due to the low α/β ratio of prostate cancer in comparison to surrounding tissues, the therapeutic ratio can be maximised by delivering higher dose per fraction in fewer fractions (hypofractionation).[4]

Hypofractionated prostate radiotherapy

Randomised trials of moderately hypofractionated (2.4-3.4 Gy per fraction) compared with conventional dose fractionation have shown non-inferior biochemical control and toxicity outcomes when using isoeffective doses.[5] The HYPO-RT-PC phase III randomised trial compared ultra-hypofractionation (42.7 Gy in seven fractions) and conventional fractionation (78 Gy in 39 fractions) delivered using 3D conformal radiotherapy for intermediate and high- risk prostate cancer. This showed a mild increase in acute grade 2 or greater genitourinary (GU) toxicity in the ultra-hypofractionated group (28%) compared with conventional fractionation (23%) at the end of treatment and at GU toxicity at 1 year with 6% and 2 % respectively.[6] This was likely due to the condensed treatment time. However, there was no difference in the long-term genitourinary (5% and 5% respectively) or gastrointestinal toxicity (1% and 4% respectively). In both arms, erectile function decreased from almost 70% at baseline to 35% at 5 years. There was no difference in disease-free survival at 5 years (84% for both arms), with the trial reporting that ultra-hypofractionated (≥5Gy per fraction) prostate radiotherapy was non-inferior to conventional fractionation. The PACE-B phase III randomised trial comparing conventionally fractionated or moderately hypofractionated radiotherapy using intensity modulated radiation therapy (IMRT) with stereotactic body radiotherapy (SBRT) using ultra-hypofractionated doses (7.25 Gy per fraction) reported no increase in acute toxicity with ultra-hypofractionation,[7] with long term cancer control and toxicity results pending.

Prostate SBRT toxicity

SBRT for definitive prostate cancer treatment has been used for over two decades, with increasing use particularly in low and intermediate risk patients.[8] Prospective series of over 6,000 patients have reported 7-year biochemical control rates of 93% with late grade 3 or worse genitourinary and gastrointestinal toxicity rates of 2.0% and 1.1% respectively, mostly using 5 fractions.[9] In patients who receive standard SBRT, acute toxicity side effects are common as demonstrated in the PACE-B trial,[7] where 10% of patients receiving SBRT experienced acute Grade 2 or worse gastrointestinal (GI) toxicity and 23% of patients experienced acute Grade 2 or worse genitourinary toxicity. In comparison, studies evaluating conventionally fractionated prostate radiotherapy have shown that acute low grade urinary and rectal toxicity do occur but also largely improve by 6 months.[10,11] Rectal toxicity has been shown to be strongly correlated with the dose and volume of rectal wall receiving radiation.[12] Even small increases in radiation dose can increase morbidity. When comparing 35 Gy and 36.25 Gy in 5 fractions for low and intermediate risk prostate cancer, a small percentage (1.7%) of patients receiving the higher dose experienced Grade 3 genitourinary toxicity compared with 0% for those receiving the lower dose. However no statistical difference was seen in terms of biochemical disease free survival.[10] This is in contrast to a phase 1 dose escalation study by Zelefsky et al.[13] which showed no significant difference in terms in terms of GU and GI toxicities when comparing 32.5, 35, 37.5 and 40 Gy over 5 fractions. A trend towards increased genitourinary toxicity was however reported in the higher dose groups, along with improved biochemical and 2-year biopsy control. A limitation of this study was the small sample size of 35 patients per dose group.

Sexual dysfunction is common post-SBRT, with a gradual decrease in mean change in sexual summary score of up to 11.8 points below baseline on the Expanded Prostate Cancer Index Composite (EPIC)-26 questionnaire, 24 months post treatment for a group of patients with low, intermediate and high risk disease receiving either 35 Gy or 36.25 Gy prostate SBRT without androgen deprivation therapy.[14] Another study followed 97 men post SBRT who were able to achieve an erection for sexual intercourse at baseline. Overall they reported a decrease of 18.3 points on the EPIC-26 questionnaire and a decrease in potency to 54.4% over the 2 years following 5 fractions of 35-36.25 Gy SBRT.[15] Furthermore, 4 patients who received 29.5 Gy to >25% of the penile bulb were impotent 2 years post treatment. This suggests that radiation damage to the penile bulb and potentially neurovascular bundles may lead to subsequent erectile dysfunction, which was also seen in studies of conventionally fractionated and moderately hypofractionated radiotherapy.[16,17] Other studies reported erectile function preservation rates of approximately 50% after SBRT with continued decline between two and five years.[18,19] This decline was comparable to other forms of radiotherapy including external beam, high dose rate brachytherapy boost and low dose rate brachytherapy. Planning studies of conventionally or moderately hypofractionated prostate radiotherapy have reported the dosimetric feasibility of neurovascular bundle, corpora cavernosa and internal pudendal artery sparing, in order to reduce the risk of sexual dysfunction.[20-22]

Focal therapy for prostate cancer

Given that patients with low risk disease can progress during active surveillance with a potentially higher rate of clinical progression compared to immediate treatment, this option can be stressful for some. With this in mind, the option of focal therapy has been explored; to ablate the prostate cancer when it is localised and before it invades healthy tissue outside the prostate. By undertaking focal therapy and limiting damage to surrounding tissue it is hypothesised that there will be less treatment related side effects to surrounding organs. Energy sources used to create focal tissue destruction include high frequency ultrasound, cryotherapy, photodynamic therapy, laser and irreversible electroporation.[23] A limitation to these focal therapies is the difficulty in visualising and localising the prostate lesion during treatment. Poor visualisation of tumour during treatment could potentially lead to the tumour being insufficiently ablated, or the risk that unnecessary dosage is delivered to the organs at risk (OAR). Planning studies of focal brachytherapy have reported lower OAR doses compared to whole gland brachytherapy,[24-27] although clinical studies have reported lower than expected biochemical and local control.[28,29] In a study by King et al.[28] patients with intermediate risk prostate cancer who underwent focal brachytherapy to the peripheral zone had a 10-year local recurrence of 22.5%. Limitations of this study included the use of only a 0.5 Tesla MRI, in comparison with higher diagnostic imaging using 1.5 or 3.0 Tesla, and the low rate (18%) of 12 core pre-treatment biopsy to detect patients with secondary lesions within the prostate. Therefore it is possible that a percentage of the recurrence was due to inadequate treatment at baseline. A series of 30 patients treated with single dose of 19 Gy HDR brachytherapy to the tumour with a 5mm margin using 1.5T MRI reported a 4-year biochemical disease free survival of 70%, with 9 local recurrences.[29] This is similar to the lower biochemical control rates seen with single dose whole gland brachytherapy compared with multifraction brachytherapy,[30] even with the addition of an MR-guided boost.[31]

Focal prostate SBRT

In view of the steep dose fall-off seen with SBRT,[32] focal radiotherapy directed at the tumour rather than the entire gland has the potential to improve outcomes and reduce side effects. An SBRT planning study of 40 Gy in 5 fractions demonstrated that hemigland (half a gland) treatments offer significant reductions in radiation dose

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to the urethra, rectum and bladder compared to whole gland SBRT. For the rectum there was a reduction ranging from 12-79% for $V_{80\text{-}90\%}$, for the bladder a reduction of 12-61% $V_{50\%}$ (where V equals volume of the structure and $_{x\%}$ equals the percentage of the prescription dose). The maximum dose delivered to the urethra was reduced from 43.0 Gy to 39.7 Gy, mean penile bulb dose decreased from 13.3 Gy to 9.2 Gy and the contralateral neurovascular bundle decreased from 40.2 Gy to 19.3 Gy.[33]

MRI in prostate radiotherapy

MRI is an imaging modality that has both the spatial resolution and soft tissue contrast to accurately characterise individual tumours within the prostate.[34,35] The majority (90%) of significant prostate cancers are visible on MRI.[36] MRI of the prostate allows the treating physician to identify the dominant nodules requiring treatment,[37] with a study by Harvey et al.[38] showing low interobserver variability of the dominant nodule on multiparametric (mp)MRI. MRI-guided radiation also allows radiation doses targeted specifically at visible prostate lesions with decreased planned treatment volume (PTV margins).[39] This is particularly important in prostate radiotherapy for the high dose constraints for the rectum, neurovascular bundles, and bladder although there can be interobserver variation in target and organ at risk delineation.[38,40] However, MRI can underestimate gross tumour volume from 18% when using dynamic contrast enhanced (DCE) sequences and up to 58% with diffusion weighted imaging (DWI).[41] This is where prostate specific membrane antigen PET (PSMA-PET) may improve target volume delineation in addition to MRI.[42]

MRI-guided radiotherapy

The MRI -linear accelerator systems provide what has long been considered the “holy grail” of radiotherapy delivery, the integration of an MRI scanner that can provide clinical quality imaging with a modern linear accelerator.[43] The Elekta (Elekta, Stockholm, Sweden) MR Linac is a 1.5T, 7MV; 70cm closed bore MRI linear accelerator. Adaptive Radiation Therapy (ART) capabilities include: adapt to position (ATP) and adapt to shape (ATS). The ATP method is based on the pre-treatment CT to find the isocentre of the tumour based on the online patient position, while the ATS method uses daily recontouring and plan adaptation based on the patient anatomy of the day. The MR-Linac has the potential to visualise and adapt to anatomical changes of the tumour within the course of the radiotherapy treatment regime. The daily re-optimisation may include adaptation of segments, optimisation of weights from segments, optimisation of weights from fluence, optimisation of weights and shapes from segments or optimisation of weights and shapes from fluence.[44] The treatment process begins with the clinical team acquiring a set of MRI images, identifying targets of tissue to be treated, and drawing treatment contours. The treatment planning system computes the dosimetry and number of fractions required to treat the planning target volume while minimising the dose to surrounding healthy tissues. Dynamic MRI images taken during the actual treatment provide higher quality images of target lesions compared to cone beam CT based therapy and quantitative, real-time assessments of tissue changes.[43] Due to this real-time nature, therapy can pause if significant movement of the target area or OAR occur and only recommence when the target volume comes fully back in alignment or treatment is adjusted otherwise.

MR-guided prostate SBRT

MR guided prostate SBRT using an MR linear accelerator has been shown to be feasible using both ViewRay MRIdian.[39,45,46] and Philips Elekta Unity[47] technologies. Amsterdam University Medical Centre (VUMC) reported outcomes of 101 patients treated with prostate stereotactic ablative radiotherapy (SABR) using 36.25 Gy in 5 fractions on the MRIdian, with grade ≥2 early GU and GI toxicity of 23.8% and 5.0% and early grade 3 GU toxicity of 0% (CTCAE) and 5.9% Radiation Therapy Oncology Group (RTOG). They reported a peak GU grade ≥2 toxicity of 19.8% at the end of MR guided radiotherapy (MRgRT), followed by a return to the baseline average score at 3-month follow-up.[46] Long term follow up showed clinician-reported grade ≥2 GU toxicity remaining between 3.1% and 5.1% and no grade ≥2 GI toxicity, with sexual function not reported due to 82% of patients receiving hormonal therapy.[39]

Sacro Cuore Don Calabria Hospital reported outcomes of 25 patients treated with prostate SABR using 35Gy in 5 fractions on the Unity, with acute grade 2 GU and GI toxicity of 12% and 4% respectively.[47] 9 patients with unfavourable intermediate risk prostate cancer were treated with androgen deprivation therapy, with no significant decline in erectile function using the International Index of Erectile Function (IIEF)-5 questionnaire being reported at the end of radiotherapy.

Prostate SBRT dose fractionation

While 5 fractions has been most commonly used in prostate SBRT, reducing the number of fractions can increase the convenience of treatment and potentially improve patient reported outcomes. The Sunnybrook group reported a comparison of single arm prospective trials using 26 Gy delivered in 2 fractions, 1 week apart and 40 Gy in 5 fractions over 2 to 5 weeks. With a median follow up of approximately 5 years in both trials, they reported comparable control rates and improved low grade bowel (17.8% vs 42.3%), moderate grade bowel (7.1% vs 24%) and sexual (15.3% vs 29.2%) patient reported outcomes with 2 and 5 fractions respectively.[48] A difference in treatment protocol that may have impacted the outcomes was the planning target volume margins. In the 5-fraction protocol, the clinical target volume (CTV) was the prostate with a PTV margin of 5mm. In the 26 Gy protocol, the CTV was the prostate with a PTV margin of 3mm, and an endorectal immobilisation system was used to reduce movement of the prostate. The use of an MR-Linac may permit treatment with these decreased PTV margins to be delivered accurately, with real time tracking of the dominant nodule.

Conclusion and direction for future research

There have been limited studies reporting on the feasibility, effectiveness and potential benefits of the Elekta Unity MR-Linac in the treatment of localised prostate cancer. Currently there is the need for large studies in this area looking at the use of the MR-Linac including randomised controlled trials comparing the MR-Linac to other delivery systems reporting on extended follow up. One example is the MIRAGE trial (NCT04384770) a phase III randomized trial comparing CT-guided SABR with MR-guided SABR for localized prostate cancer with a primary endpoint of acute grade ≥2 genitourinary toxicity.[49]

The MR-Linac shows much promise in improving patient outcomes for localised prostate cancer. It has the potential to improve focal radiation delivery, reducing radiation margins and thereby toxicity to the surrounding organs at risk, and trials of focal MR guided radiotherapy for prostate cancer are warranted.

Conflicts of interest

The authors declare that they have no competing interests in relation to this paper.

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