

**Exploring the role of naturally occurring prostate
calcifications as an alternative to surgically implanted
fiducial markers for image guided radiotherapy**

Final Report

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Evidence Brief

Why did we start?

Prostate radiotherapy is a potentially curative treatment for localised prostate cancer. Accuracy in treatment delivery is paramount in achieving tumour control and minimising toxicity. Targeting the prostate gland can be challenging because of poor soft tissue contrast associated with used Cone beam CT (CBCT) which is a widely used image guided radiotherapy (IGRT) technique. Surgically implanted fiducial markers (FM) are often employed to enhance visibility of the prostate during treatment. We investigated the potential of naturally occurring prostate calcifications (PCs) as an alternative to FM for IGRT. This approach could potentially eliminate the need for a surgical procedure along with the associated costs and risks to the patient while ensuring maximum accuracy in radiotherapy treatment delivery. There is very limited published evidence currently available on using this approach.

What did we do?

- We investigated the incidence of PCs in the local prostate radiotherapy population
- We designed and completed a prospective clinical trial to investigate the feasibility of using PCs to target the prostate during radiotherapy delivery. 58 patients were recruited to the study, 30 of whom had prostate calcifications.
- We assessed patient reported outcomes (PROMs) on their experience of surgical implantation of FM.

What answer did we get?

- From our retrospective and prospective data between 55% and 85% of prostate radiotherapy patients have PCs visible on radiotherapy images.
- CT confirmed intra-prostatic PCs (25%) are equivalent to FMs as a surrogate for the prostate. In general all PCs in or close to the prostate are a feasible alternative to FMs when used in conjunction with CBCT.
- PC guided EBRT potentially eliminates the need for an invasive procedure, the associated side effects and costs for at least 25% of prostate radiotherapy patients.

What should be done now?

- Further investigation is needed on methods for timely and reliable detection of PCs if they are to replace FMs. The potential of magnetic resonance imaging techniques to detect PCs is particularly relevant given its established role in the diagnosis and staging of prostate cancer.
- Further research into how strategic use of PCs and FMs may be used to target areas of dominant malignancy within the prostate gland.
- Further studies collecting prospective patient reported outcome data on the impact of FM implantation is warranted.
- In the absence of FMs, PCs can be utilised as an alternative with an appropriately developed CBCT imaging protocol to enhance prostate IGRT.
- A clinical implementation phase along with a prospective audit of practice would be required to enable roll-out, ensure consistent practice and reporting of treatment accuracy.

1. Background

Radiotherapy for Localised Prostate Cancer

External beam radiotherapy (EBRT) directs a pre-defined dose of high energy X-ray beams to the prostate from outside the body using a linear accelerator. Advanced radiotherapy techniques such as Intensity Modulated radiotherapy (IMRT) and Image Guided Radiotherapy (IGRT) have facilitated dose escalation studies, which demonstrate a correlation of increased dose with disease free survival. [1][2] However, dose escalation is limited by a number of factors including uncertainties in daily treatment set-up and internal organ motion. These uncertainties are encompassed by margins added to the target during treatment planning. [3][4]

The philosophy of applying margins ensures that the prostate is always included in the high dose region during treatment. However creating margins also increases the volume of normal tissue exposed to radiation. This increases the likelihood or severity of early and late treatment related side effects. The aim of IGRT is to ensure the dose is delivered as planned so that the benefits of reduced margins/dose escalation can be realised safely in the clinic.

Imaging the prostate during radiotherapy

The prostate gland can be difficult to visualise accurately using the imaging modalities currently available for IGRT in most radiotherapy centres. These include 2D kV and 3D kV imaging solutions e.g. cone beam computed tomography (CBCT), which are not optimal soft tissue imaging modalities. Skill and experience is required in the interpretation of CBCT images and inter-observer variability in identifying the prostate has the potential to influence treatment accuracy.[5]

A common IGRT strategy is to use pelvic bony anatomy as a frame of reference to position patients as planned. This may be adequate for large homogeneous plans to the whole pelvis but is not optimal for dose escalated, Intensity modulated, hypo-fractionated or stereotactic treatments. This is mainly because bones are not a reliable surrogate for the position of the prostate. The prostate moves independently of the pelvic bones due to variations in rectum and bladder volume and movement or deformation of the prostate itself. [6][7][8] [9]

Fiducial Marker IGRT

Another IGRT strategy involves the use of radio-opaque fiducial markers surgically implanted into the prostate. These are visible on most imaging modalities in use for IGRT. They facilitate efficient verification of the prostate and its varying position. Their clinical use is widely reported and encouraged particularly for highly conformal techniques employing reduced planning margins.[7] [10][11][12][13][14][15]

Markers usually measure between 1-2mm diameter and up to 5mm in length and are available in various compositions, the most commonly used being gold or gold alloy.

Fiducial marker (FM) implantation requires an additional hospital attendance for a surgical procedure. Up to 4 markers are inserted into the prostate. The procedure is carried out under trans-rectal ultrasound (TRUS) guidance and markers are implanted either trans-rectally or trans-perineally. The procedure carries risks similar to that associated with prostate biopsy e.g.

pain, bleeding and infection.[16] The procedure requires time, expertise and resources. Fiducial markers, local anaesthetic, antibiotics, clinical time, resources and expertise required all contribute to the overall cost of the procedure.

Prostate calcifications

Prostate calcifications are reported to be present in almost 90% of prostatectomy specimens [17] and it is estimated that between 28 % and 35% of prostate radiotherapy patients have calcifications visible on CBCT. [18]. Patients who have prostate calcifications are often asymptomatic and they are often detected co-incidentally on radiological images. Diagnosis can be based on clinical, histological or radiological findings and they present as small ovoid or round bodies impregnated with calcium phosphate and calcium carbonate. [19]

There is limited peer-reviewed data on naturally occurring prostate calcifications and their potential role in IGRT. Based on data from 4 patients it has been reported that calcifications are stable in relation to the position of implanted markers and that it may be feasible to use calcifications for image guidance. [18] From a retrospective study of 10 patients another group concluded that centrally positioned prostate calcifications may be used for prostate radiotherapy image guidance. [20] To date there is only 1 prospective study on the use of calcifications for prostate IGRT. From data on 9 patients Sbai et al concluded that resulting set-up data were similar to data from other studies reported using FMs. [21]

2. Aims & Objectives

Aim: To establish if naturally occurring prostate calcifications can be used as a surrogate for the position of the prostate in the same way as surgically implanted FMs.

Objectives

- I. To determine if it is feasible to use prostate calcifications as an alternative to surgically implanted FMs for image guided radiotherapy
- II. Determine treatment accuracy in relation to varying imaging reference parameters
- III. Assess patients experience of fiducial marker implantation

3. Methods

- I. A retrospective radiological study of the incidence of PCs in a sample of 254 prostate radiotherapy patients was completed
- II. Subsequently a prospective clinical study, CASPIR (Calcifications as an alternative to surgically implanted markers for prostate image guided radiotherapy) was designed. All patients had FM IGRT. In those with PCs, this design facilitated a direct comparison of FMs with PCs for the purpose of IGRT.
- III. A study of geometric uncertainties associated with patient set-up formed the core focus of this study and the analysis.
- IV. Patient reported outcome following FM implantation was assessed with the use of patient questionnaire.

4. Personal and Public Involvement (PPI)

This development of this study has benefitted from PPI via the Northern Ireland Cancer Research Consumer Forum (NICRCF) since 2013, prior to the initial PHA application, as per initial progress

report. I have maintained this dialogue with the NICRCF and have become involved with Prostate Cancer Research PPI Advisory Group.

Progress reports have been presented and discussed annually to this group in April 2016, 27th April 2017 and 2nd May 2018. This dialogue has focussed mainly on the CASPIR study and the potential impact of this. This group provided insight into perhaps why some patients are willing to participate and others are not.

5. Summary of findings

TP implantation of FMs is tolerable and safe for the majority of patients. However 46% of patients in our study experienced mild to moderate pain.

A significant proportion (up to 85%) of patients with PCa have calculi detectable on pre-radiotherapy imaging. 99% of those detected on CT were subsequently detected on CBCT and remained visible at the end of a course of radiotherapy.

PC occur most frequently in the posterior aspects of the mid-gland and apex which may enhance image analysis at the prostate/rectal interface.

CT confirmed PCs provide a reliable surrogate for the prostate and are a feasible alternative to FMs.

Between 50% -85% of localised PCa radiotherapy patients may benefit from PC CBCT guided EBRT.

Further investigation is needed on methods for timely reliable detection of PC if they are to replace FMs.

Adoption of PC guided EBRT potentially eliminates the need for an invasive procedure, and associated side effects and costs.

6. Conclusion

Our research establishes evidence for the use of PCs a reliable alternative to FMs. In the absence of FMs CT confirmed intra prostatic PCs provide a good surrogate for the prostate and a comparable substitute to FMs.

7. Practice and Policy Implications/Recommendations

With a view to reducing invasive procedures, associated risks & resources and the use of prophylactic anti-biotic therapy:

- I. Where FMs would ordinarily be employed, the presence of PCs should be considered as an alternative.
- II. If the number of PCs is considered inadequate, fewer FMs should be employed and strategically placed in relation the PCs.

8. Pathway to Impact

The findings from this research could be put into practice clinically if provision is made for an appropriate implementation phase. This would require as a minimum:

- I. A project lead/researcher
- II. Development/updating of associated protocols, procedures and patient pathways
- III. A programme for staff training
- IV. A pilot phase for initial clinical implementation in parallel with prospective clinical audit of practice
- V. Achievable within 2 years

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