

## Fiducial Markers in Image-guided Radiotherapy of the Prostate

a report by

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Fiducial markers are emerging as a standard tool for image-guided radiotherapy (IGRT). The markers are implantable devices designed to act as reliable surrogates for imaging anatomic structures of interest. Fiducial marker techniques were originally developed in the pre-conformal radiotherapy era for positional verification of tissues that were not easily visualized using portal X-ray film imaging for patient alignment. Soft tissue structures that were relatively mobile could be more readily seen when radio-opaque seeds or wires were implanted in or near organs of interest. However, since comparatively large margins around target volumes were used, dose delivery limitations overshadowed imaging accuracy. In addition, routine and efficient 'online' (at the time of treatment) implementation of patient set-up error analysis and patient repositioning was problematic in the past.

Modern radiotherapy increasingly utilizes conformal delivery techniques, which necessitate more accurate patient positioning and tumor targeting.<sup>1</sup> Brought about by mechanical and computing advances, the ability to deliver radiation doses to the tumor while sparing normal tissue using 3-D conformal radiotherapy (3D-CRT), intensity modulated radiotherapy (IMRT) or other conformal treatments, such as proton therapy, allows the potential for reduction of toxicity and—through careful dose escalation—potentially better outcomes. It is hoped that by keeping 'tight margins' around target volumes these dual goals may be attained.

As a practical matter, improved dose delivery precision necessitates a higher degree of accuracy in targeting the tumor (target delineation) and aligning the patient so as to reproducibly confirm that the tumor is in the same place in 3-D space as the prescribed conformal dose distribution throughout therapy (positional verification). However, since even small geometric deviations from the treatment plan may result in substantial changes in dose distribution,<sup>2</sup> margin reduction must be matched with IGRT techniques lest margin reduction result in poorer clinical outcomes.<sup>3</sup>

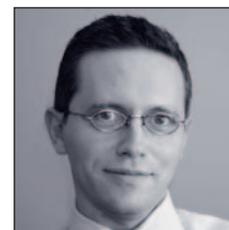
While fiducial markers have been implemented in head and neck, gastrointestinal, hepatic, and other sites, the vast majority of existing data has been generated in prostate

cancer and, for the purposes of this manuscript, this organ site will be exclusively focused on. Prostate cancer demonstrates a dose-response profile such that increasing delivery of dose to tumor is associated with better outcomes. However, prostate radiotherapy presents several unique issues for which fiducial markers may be a useful tool. The prostate is difficult to image using standard X-ray films, lies in proximity to hollow organs (the bladder and rectum), which are at risk of radiotherapy-induced toxicity, and may be displaced due to filling of these adjacent organs. As such, the prostate represents a 'moving target' as changes in bladder and bowel filling can displace the prostate significantly between, or even during, radiotherapy fractions.<sup>4</sup> Since the prostate is not attached directly to bony anatomy, prostate motion differs substantially from pelvic bony anatomic position. Adding larger margins to the prostate increases dose to bladder and rectum, improving target coverage but also increasing the probability of toxicity: this is a less than optimal solution to ensure tumor coverage. The problem is magnified when steep dose gradients such as with 3D-CRT or IMRT are employed or when dose escalation is desired.<sup>5</sup> Since gross tumor volume and microscopic extent of disease cannot be reduced, the most reasonable mechanism for reduction of margins is increased accuracy of targeting and patient alignment.<sup>6,7</sup>

For years, the concept of visualizing intra-prostatic implanted seeds has been a logistical consideration in the earliest conformal radiotherapy techniques (implant brachytherapy).<sup>8-12</sup> Indeed, several series have implanted fiducial markers during brachytherapy with  $I_{125}$  seeds in expectation of subsequent boost external beam radiotherapy.<sup>10</sup> As the concept of implanted devices for external beam targeting has evolved, numerous permutations on the fiducial marker concept have arisen. The most frequently utilized devices in most series have been gold seeds, making them suitably visualized using a variety of imaging methodologies. Typically, the seeds are cylindrical, allowing ease of insertion via a needle by transrectal ultrasound, and have surface features that prevent seed migration after insertion. Varying sizes of seed marker, including custom lengths, may be ordered. Carbon fiducials hold the promise of visibility on computed tomography (CT) imaging and producing less

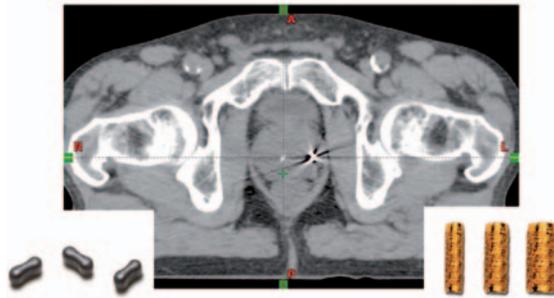


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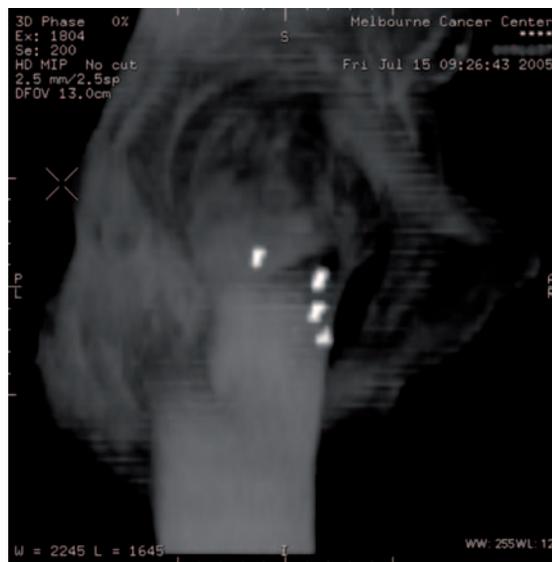


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**Figure 1: Axial CT-scan Sowing Carbon Fiducial Marker (Left Side, with Fiducial Detail in Inset) and Gold Seed Markers (Right)**



**Figure 2: Digital Reconstructed Radiograph Showing Gold Marker Seeds**



artifact as compared with gold (Civco/NMPE, Lynnwood, WA). Strings of markers on a bio-absorbable strand are available (Best Medical, Springfield, VA), as are metallic coils (Visicoil, Radiomed, Tyngsboro, MA)<sup>13</sup>. Both strings and coils are designed to span the whole of the gland and thus potentially provide a readily imaged and positionally stable surrogate. Another novel concept developed recently is encapsulation of radiofrequency transponders within implantable markers; the signal reflected by these implanted transponders can be used to wirelessly track prostate motion in realtime during therapy without reliance on radiographic imaging.<sup>14,15</sup>

While at present no established data sets have compared product usability across fiducial marker systems, a series from the University of Manchester compared marker sizes ranging from 3mm to 8mm in length, and 0.8mm to 1.1mm diameter, using electronic portal images, determining that markers <5mm in length or <0.9mm in diameter were poorly visualized.<sup>16</sup> Whether this observation holds true for a

variety of image guidance techniques (such as electronic portal imaging, cone-beam CT, orthogonal kilovoltage X-ray, ultrasound, and CT)<sup>17</sup> remains to be ascertained. As several authors have noted, the wide empiric utilization of image-guided and conformal radiotherapy techniques has, to an extent, outpaced the availability of rigorous intra- and inter-platform comparisons of technical and clinical parameters.

Accruing data regarding fiducial markers have been put forth within the radiotherapy literature. Seminal data from the University of Michigan used fiducial marker placement in concert with orthogonal port films, demonstrating a maximum displacement of 7.5mm in a single directional axis, with most offsets of 0–4mm.<sup>18,19</sup> Similarly, Crook et al. found similar directional offsets, with posterior mean offsets of 5.6mm; and inferior directional shifts averaging 5.9mm.<sup>20</sup> These early data sets also confirmed that prostate motion was not uniform and random, but exhibited a predominant directional component, related to rectal and bladder filling. Until the widespread implementation of the tight dose margins possible with IMRT, utilization remained limited to a few academic institutions. However, these early experiences using port films paved the way for future series,<sup>21</sup> and established the clinical feasibility of fiducial marker placement.<sup>19</sup> Since these initial efforts, many groups have sought to implement fiducial markers as part of processes designed to afford positional verification as well as image co-registration.<sup>14,21–28</sup>

Early adopters of seed implantation demonstrated that implementation of fiducial markers in clinical practice could be achieved with minimal incremental work flow adjustment. Over time, as with any alteration to treatment planning protocols, efficiency of use improves rapidly after an initial learning curve. At the MIMA Cancer Center in Melbourne, FL, patients arrive for an appointment three to five days before their treatment planning CT. The patient is situated in the left lateral decubitus position, and transrectal ultrasonography is used to localize the prostate gland. Four gold seeds are placed via preloaded needles and a transrectal approach near the apex, mid-gland, and left and right base positions within the prostate using sagittal ultrasound guidance without any anesthesia. At least three days are then allowed to pass before CT simulation to allow residual swelling to resolve. After placement, the patient may be readily imaged by treatment planning CT simulation, and the seeds can be observed easily on digital reconstructed radiographs. At this time, if desired, the seeds may be delineated at the same time as clinically relevant target volumes and organs at risk. The MIMA Cancer Center has recently initiated thin-slice magnetic resonance imaging (MRI) scanning of patients about one week after marker placement. Using custom MRI sequences as outlined by Huisman et al.,<sup>29</sup>

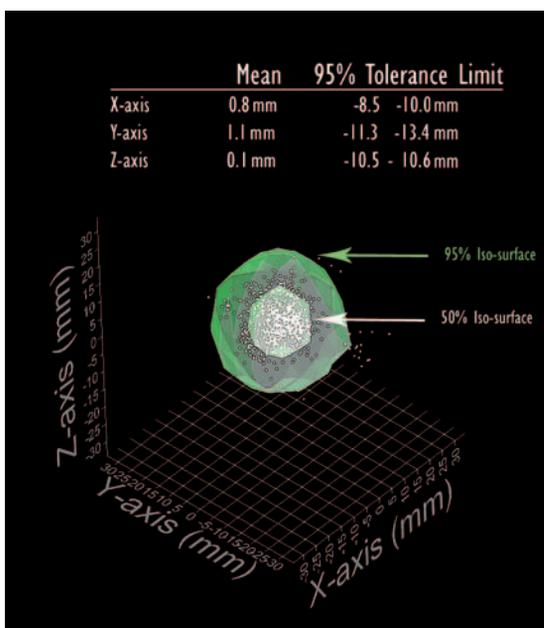
the small 1 x 3mm gold markers can be visualized on MRI and allow perfect prostate MRI-to-CT fusion. Prostate anatomy target delineation is improved with use of MRI, and the problem of registration/fusion errors (dose distributions can only be planned on CT data sets) is overcome by marker-to-marker/MRI-to-CT fusion.

Much of the work using fiducial markers was performed in order to more accurately define physical points within the prostate for imaging method comparison. In a proto-image-guidance paper, Sandler et al., in a series of 15 patients, all of whom received pelvic CT and retrograde urethrogram after transrectal ultrasound using gold seeds implanted in the prostate, demonstrated the superiority of CT-based imaging for apex localization, as well as the potential for visualizing seeds on mega-voltage CT.<sup>30</sup> Similarly, seed data was used by Malone et al. to determine that barium enemas might provide erroneous inputs for target localization.<sup>31</sup>

Since the most common alternate method in recent years has been ultrasound prostate positional verification,<sup>32</sup> the majority of method comparison series recently have compared seed and ultrasound techniques. Emerging data suggest that ultrasound systematic error is high compared with seed localization imaging platforms. Langen et al. found ultrasound alignments to exhibit a systematic differential from the marker alignments in the superior-inferior and lateral axes, with random variability equivalent to or similar to the initial set-up, and significant inter-user variability. Van den Heuvel, using five to six seeds for both ultrasound and electronic portal imaging (EPI) localization, showed significant improvement with ultrasound was obtained in only the antero-posterior dimension, with no measurable improvement in two other room axes.<sup>33</sup> In contrast, seed localization was revealed to show significant improvement in set-up capability.<sup>34</sup> Serago et al. recently compared alignment to skin marks with fiducial marker localization by EPI, ultrasound, and kilovoltage X-ray imaging. This comparison revealed ultrasound improves alignment to EPI-based positioning compared with skin marks alone, while kV fiducial marker imaging was most consistent with EPI. They conclude by noting that both megavoltage and kilovoltage imaging have similar accuracy profiles and both offer a substantial improvement over ultrasound.<sup>35</sup>

The authors' own experience with ultrasound versus seed marker prostate localization represents the largest IGRT data set thus far presented in the literature. In the first report, it was concluded that margin reduction (versus ultrasound or non-ultrasound approaches) using seed markers could be substantial. It was also concluded that versus set-up to skin marks only, an ultrasound IGRT approach offered no improvement or some slight

**Figure 3: Plot of 1,019 Daily Kilovoltage X-ray Image-guided Shifts in 40 Patients using Fiducial Seed Markers**



The 50% and 95% iso-surfaces represent a volume containing half and 95% of all 3-D shifts. Table at top shows the mean displacement and 95% iso-surface tolerance dimensions in each principal room axis (all values in mm).

worsening of set-up accuracy. As part of the investigations into method comparison of prostate imaging techniques, data suggest that ultrasound and kVp approaches have poor agreement and should not be utilized interchangeably.<sup>36</sup> Additionally, ultrasound imaging exhibited systematic error components that would necessitate comparatively larger margins to safely implement in comparison to kilovoltage seed imaging.

As previously noted, the benefits available from daily prostate alignment are only conferred when radiation dose may be preferentially delivered to target volumes while sparing adjacent structures. Target volumes typically are conceptualized using the International Commission on Radiation Units and Measurements (ICRU) nomenclature, which specifies radiographically evident tumor as gross tumor volume (GTV) and the clinically expected region of microscopic extension of tumor as the clinical target volume (CTV). Since these volumes must receive the prescribed dose in order to effect tumor control, their volumes may not be minimized without dire consequences. Practically speaking, therefore, these volumes cannot be reduced, all reduction in irradiated volumes is performed by reducing the planning target volume (PTV). The PTV, according to van Herk,<sup>37</sup> should represent "the volume, defined in treatment room coordinates, to which a prescribed dose must be delivered in order to obtain a clinically acceptable and specified probability that the

prescribed dose is actually received by the CTV, which has an uncertain location.” This safety margin is designed to conceptually account for a multitude of factors that might affect the capacity to deliver dose accurately. By reducing the degree of variability of daily positioning through seed markers, it is possible to reduce the required margins and, thus, with a smaller PTV, spare more normal tissue.

Using established ‘recipes’ for margin calculation, the authors’ group has determined that uniform PTV margins of approximately 3mm would be required to account for random and systematic error inherent a commercially available seed-marker IGRT system. In contrast, a comparison ultrasound localization system would require margins of approximately 9mm, only marginally improved from the 10–13mm margins required without image guidance.<sup>24</sup> While this finding cannot necessarily be generalized to other fiducial marker-based imaging platforms, it does suggest a possible mechanism to reduce clinical toxicity by reducing the volume irradiated to 100% of the prescribed dose to tumor.

Fiducial marker utilization is not without inherent costs, however. Pollack<sup>38</sup> notes three potential drawbacks of seed localization for prostate radiotherapy: invasiveness, automated positional registration error, and seed migration.<sup>23</sup> However, in our experience, these have not precluded utilization. Seed placement is necessarily invasive, but the short (less than three minute) transrectal

The novelty of image-guided techniques and the multiplicity of platforms have precluded a definitive determination of the clinical import of fiducial markers on clinical outcomes in radiotherapy.<sup>40</sup> Preliminary data, however, are enticing. Out of a series of 152 patients treated using fiducial marker image guidance at MIMA Cancer Center to a prescription dose of 81Gy, 98% of patients were observed experiencing no rectal toxicity (Radiation Therapy Oncology Group (RTOG) grade 0) with the remaining 2% experiencing no more than RTOG grade II rectal toxicity. No cases of grade III or greater rectal toxicity have been observed to date (as measured by Common Terminology Criteria v3.0).

While in the absence of long-term prospective outcome data the true clinical value of fiducial marker-based systems remains to be determined, some preliminary observations can be made. First, there is a substantial amount of data that demonstrates statistically significant margin reduction ability of fiducial marker-based prostate IGRT methods. Second, no other IGRT system or technique has definitively been shown to be superior to fiducial markers in regards to margin reduction. Lastly, the authors’ own preliminary data indicates a favorable toxicity profile using fiducial marker-based prostate IGRT. In the opinion of the authors, fiducial marker-based IGRT represents the state of the art in conformal prostate radiotherapy and will become (if not already) the standard of radiation medicine care in this disease site.

*Commercially available fiducial marker target localization and positional verification techniques offer an attractive premise for efforts for radiotherapy margin reduction in prostate cancer.*

insertion, even without anesthesia, has been exceedingly well tolerated by patients. System accuracy for several vendors has been measured at sub-millimeter ranges, and seed migration, while ever a concern, has not, at least in the authors’ data set, been a noticeable phenomenon. The more practical shortcomings of this, as with any technical modification, are increased time and resource costs. While fiducial marker tracking systems are more expensive, upfront hardware and staff costs of device placement and utilization must be considered. Even so, with trained personnel and implementation of resource saving techniques for placement (on-site transrectal ultrasound implantation) or daily set-up protocol modification,<sup>39</sup> many obstacles may be minimized or circumvented.

#### Conclusion

Commercially available fiducial marker target localization and positional verification techniques offer an attractive premise for efforts for radiotherapy margin reduction in prostate cancer. While the technical and dosimetric aspects of fiducial marker co-registration are attractive, future study is required to determine whether increased patient positioning accuracy may be translated into improved outcomes and/or reduced toxicity. ■

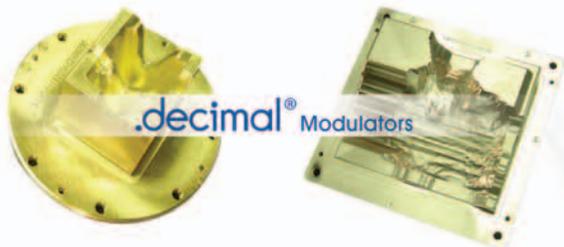
*A version of this article containing references can be found in the Reference Section on the website supporting this briefing ([www.touchoncologicaldisease.com](http://www.touchoncologicaldisease.com)).*

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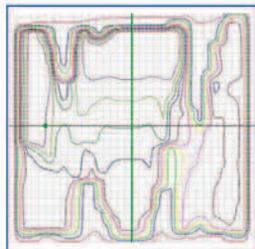
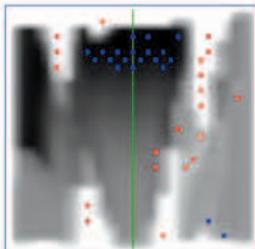
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1. Import the image by one button
2. Auto contour the organ, such as skin, lung, spinal-cord, and eyes
3. Contour the target
4. Define dose constraints for organs and target
5. Auto optimize dose intensity map
6. Create compensators and export to .decimal by E-mail
7. Receive the Solid Filter by mail *(next day)*
8. Verify and treat



## IMRT QA

1. Load the IMRT Plan to the phantom;
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3. Radiate and compare the dose distribution.



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Contour Table: Wacom 17"

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