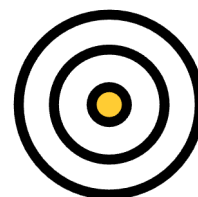


Why fiducial markers?

Increased Accuracy



98% CTV dose coverage was achieved using fiducial markers, comparable to using MR-Linac. When using CBCT without fiducial markers CTV dose coverage was 62%¹.

Reduced side effects



50% reduction in acute grade ≥ 2 GU toxicity has been observed when reducing PTV margins from 4 mm to 2 mm for prostate SBRT². Real-time tracking with fiducial markers may enable the use of such margins³.

Improved treatment outcome



97% biochemical control at 3 years in high-risk patients when positioned using fiducial markers vs. 78% without IGRT⁴.

1. Nicosia L, et al. Acta Oncol. 2021;60(2):215–22. <https://doi.org/10.1080/0284186X.2020.1821090>

2. Neylon J, et al. Int J Radiat Oncol Biol Phys. 2024;118(5):1181–91. <https://doi.org/10.1016/j.ijrobp.2023.12.035>

3. Ghadjar P, et al. Radiother Oncol. 2019;141:5–13. <https://doi.org/10.1016/j.radonc.2019.08.027>

4. Zelefsky MJ, et al. Int J Radiat Oncol Biol Phys. 2012;84(1):125–9. <https://doi.org/10.1016/j.ijrobp.2011.11.047>

Why fiducial markers?

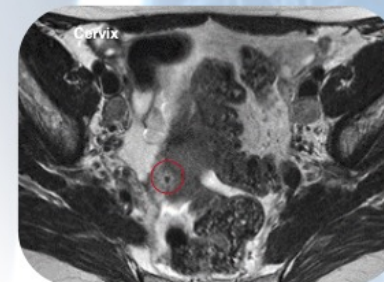
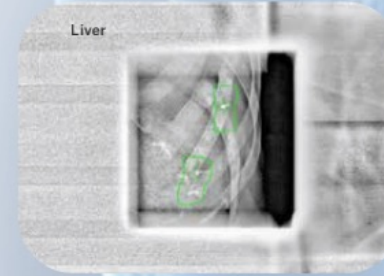
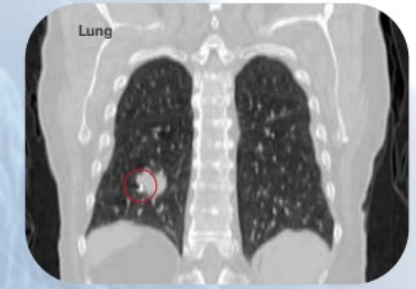
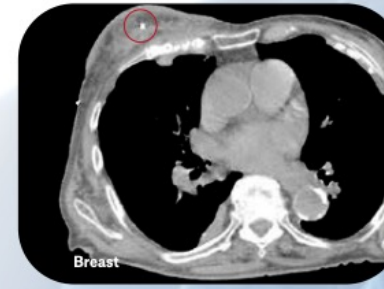
Fiducial markers are small, radiopaque objects (typically made of gold) that are implanted within or near the target area (such as a tumor) before the radiotherapy treatment begins.

Fiducial markers are used in Image Guided Radiotherapy (IGRT) to improve the accuracy and precision of treatment delivery.

These markers serve as reference points or landmarks that can be easily identified on imaging scans, helping to ensure the precise positioning of the patient and the accurate delivery of radiation.

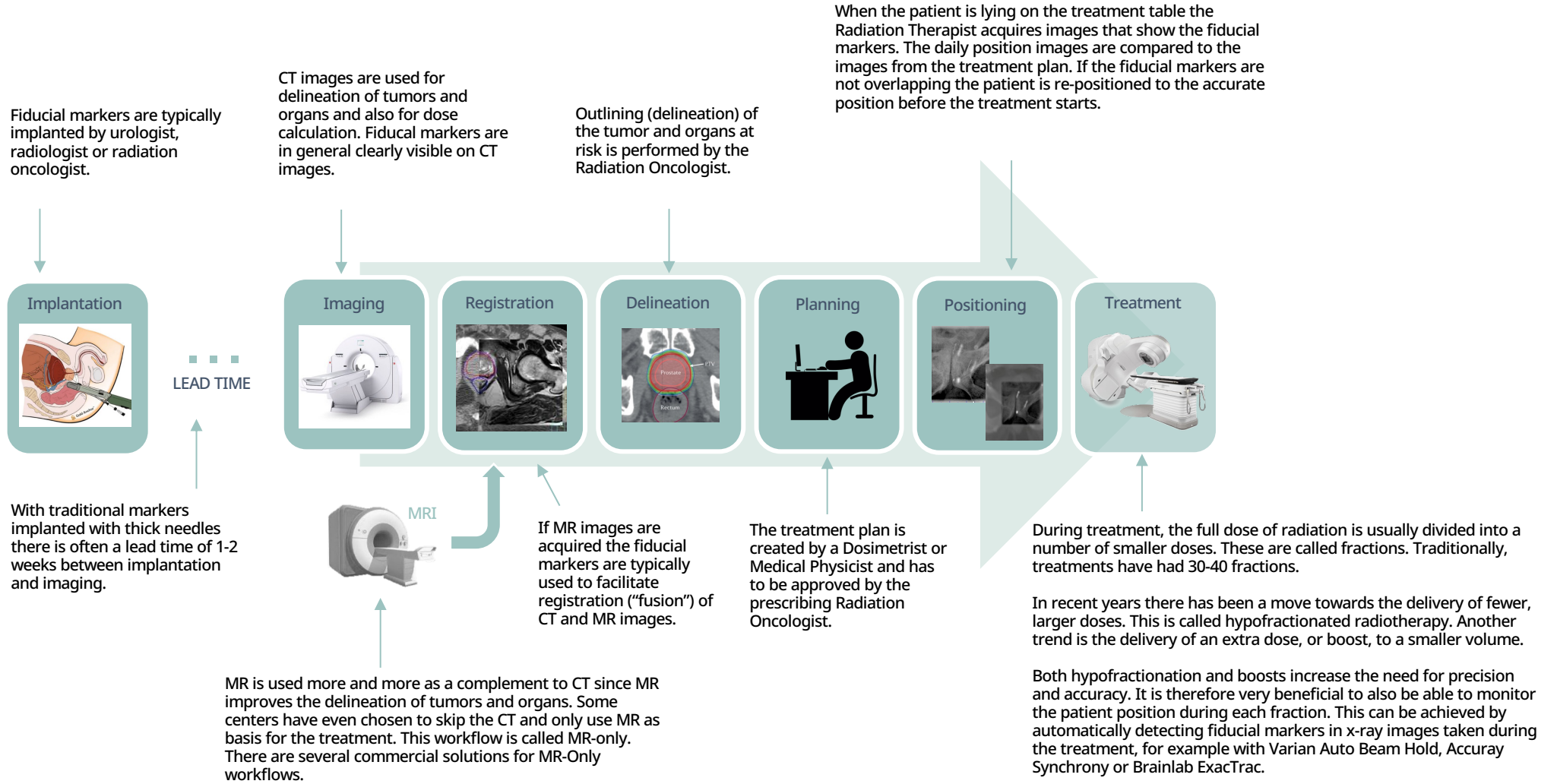
Functioning as reliable reference points, these markers account for the natural movement of the tumor and surrounding organs caused by physiological activities like breathing, bowel movements, and changes in bladder volume. This movement can be precisely tracked on imaging scans thanks to the markers, ensuring the tumor's exact positioning and the precise delivery of radiation to the intended area.

Using fiducial markers for radiotherapy treatments have proven to improve treatment outcomes in terms of reduced side effects and tumor control.



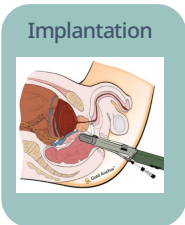
Fiducial markers in radiotherapy are used for:

- >> Accurate image registration and patient positioning
- >> Intrafraction motion management



Gold Anchor offers several important benefits throughout the treatment process

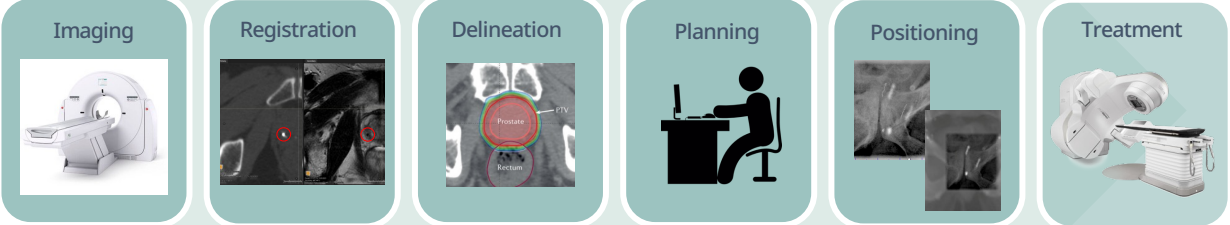
Gold Anchor markers are implanted with very thin needles. This reduces the risks and pain associated with the implantation.



LEAD TIME

With Gold Anchor there is no lead time between implantation and imaging. The thin needles and unique folding marker design provides superior attachment to tissue, enabling CT/MR directly after implantation.

The Gold Anchor markers are relatively small and therefore produce limited CT artifacts (artifacts make target delineation more difficult).



The Gold Anchor markers are made out of a unique and patented alloy of 98.5% gold and 1.5% iron. The iron enhances the MR visibility, which helps improve the registration ("fusion") of CT and MR images.

The Gold Anchor markers are clearly visible with onboard kV imaging, both on 2D and 3D (CBCT = Cone-Beam CT) images, since they are made of a high-density material. Positioning with Gold Anchor is quick and easy. Most systems can automatically detect Gold Anchor markers.

During treatment the Gold Anchor markers can be tracked with kV-images to monitor intrafraction motion. This is especially beneficial for hypofractionated or SBRT treatments where precision is extremely important. If the markers are found outside the pre-set boundaries the beam can be paused.

What does the guidelines say about fiducial markers?

The European Society for Radiotherapy & Oncology (ESTRO) has published an article: “ESTRO ACROP consensus guideline on the use of image guided radiation therapy for localized prostate cancer”¹ that states:

Recommended technology

In general, systems using markers (single/stereoscopic X-ray imaging or CBCT) have been reported to be able to detect smaller shifts than CT-based IGRT using soft tissue matching. Nonetheless, since the differences are small, we conclude that IGRT to account for interfractional prostate movement for conventionally fractionated and moderately hypofractionated EBRT as a minimum standard must be based on either fiducial markers or CT-based approaches with soft-tissue matching.

Because CT-based IGRT offers the advantage of visualizing the rotations and deformations of the prostate and seminal vesicles, a combination of fiducial markers with CT-based approaches is preferred. When the lymph nodes are part of the treatment, volumetric imaging (e.g. CBCT) is highly recommended.

Combining implanted fiducial markers with CBCT may help to reduce inter-observer variability compared to soft-tissue alignment and thus facilitate adaptive strategies.

As far as intra-fraction motion is concerned, only selected systems, such as electromagnetic transponders or single/stereoscopic X-ray imaging of implanted markers, may monitor the prostate position during treatment.

1) Source: Pirus Ghadjar, Claudio Fiorino, Per Munck af Rosenschöld, Michael Pinkawa, Thomas Zilli, Uulke A. van der Heide. ESTRO ACROP consensus guideline on the use of image guided radiation therapy for localized prostate cancer. Radiotherapy and Oncology., 2019 Dec; 141:5-13. (<https://doi.org/10.1016/j.radonc.2019.08.027>)

What does the guidelines say about fiducial markers?

The American Society for Radiation Oncology (ASTRO is the largest radiation oncology society in the USA) promotes fiducial markers as an important image guidance tool for SBRT (Stereotactic Body Radiation Therapy), both for pre-treatment positioning and for intra-fraction motion management. An ASTRO white paper¹ says:

SRS/SBRT treatment requires precision obtained through image-guided localization. Ideally, this guidance should involve tumor-based positioning at the start of each treatment fraction as geometric accuracy crucial to the safe delivery of each treatment. In the absence of direct tumor localization, reliable soft tissue surrogates (e.g., implanted fiducial markers), may be necessary as a means of estimating position. With SBRT, conventional radiographic localization based on bony anatomy is generally insufficient to meet the precision demands of stereotactic treatments for soft tissue targets.

In addition to pretreatment positioning, the management of intra-fraction patient movement and physiological motions (e.g., breathing) must be accounted for. Some examples include in-room surface monitoring systems, fluoroscopic observation, implanted radiographic markers and electromagnetic transponders, external gating systems, and external interventional mechanisms (e.g., abdominal compression and active breathing control systems).

Reduced margins with fiducial marker tracking

With the ongoing global trend of using SBRT the target area and the margins used for the radiotherapy treatment becomes critical to avoid healthy tissue being exposed to high doses of radiation. Just one movement during a fraction with a high dose can cause both underdosage of the target volume as well as excessive toxicity in healthy tissue.

The table to the right is from the above mentioned “ESTRO ACROP consensus guideline on the use of image guided radiation therapy for localized prostate cancer”¹.

The table shows that when using the “On-line + tracking” correction protocol the margins can be reduced while still delivering an adequate radiation dose.

Using fiducial markers is currently the most accessible and economical way of tracking motion in real-time during treatment.

Table 3

Examples for target margins for prostate, seminal vesicles and pelvic node according to IGRT approaches (off-line, on-line, on-line with prostate tracking).

Correction protocol	Margins (mm)		
	Prostate	Seminal Vesicles*	Pelvic Nodes*
Off-line**	LR: 5–7 AP: 7–9 CC: 7–9	LR: 7–9 AP: 8–12 CC: 8–12	LR: 7–9 AP: 7–9 CC: 7–9
On-line	Iso: 4–6	LR: 5–6 AP: 7–9 CC: 7–9	LR: 7–8 AP: 7–8 CC: 7–8
On-line + tracking	Iso: 2–4	N/A	N/A

Iso = isotropic; N/A: not applicable; LR: left–right; AP: anterior–posterior; CC: cranial–caudal; *based on prostate matching; **without further corrections after the first correction of systematic error

1) Source: Pirus Ghadjar, Claudio Fiorino, Per Munck af Rosenschöld, Michael Pinkawa, Thomas Zilli, Uulke A. van der Heide. ESTRO ACROP consensus guideline on the use of image guided radiation therapy for localized prostate cancer. Radiotherapy and Oncology., 2019 Dec; 141:5-13. (<https://doi.org/10.1016/j.radonc.2019.08.027>)

Several trends are leading to an increased use of fiducial markers

On-board imaging

- Enables fiducial markers to be visualized on orthogonal kV-images or cone-beam CT for the positioning of soft tissue targets.
- Most treatment systems offers automatic kV or Cone-beam CT-matching of fiducial markers at patient setup which speeds up the positioning.

SBRT / SABR Hypofractionation

- SBRT requires image-guided localization and conventional radiographic localization based on bony anatomy is generally insufficient for SBRT of soft tissue targets*.
- Most current prostate SBRT publications either require or strongly recommend the use of markers due to the increased precision (for ex. PACE-B and HYPO-RT-PC).

Intrafraction Motion Management

- Several systems offers real-time tracking of fiducial markers by taking continuous kV-images during each fraction, a software is used to identify and track the position of the fiducials;
- Should the markers be detected outside the pre-set boundaries the treatment can be stopped, and the patient can be repositioned again.

MRI-based target delineation

- Improves target planning. However, requires image fusion of MR and CT images or MR-only workflow.
- MRI-compatible fiducial markers can facilitate image fusion between CT and MR images, as well as the registration of synthetic CT images to MR images for improved delineation.

Increased safety focus

- Inspires search for opportunities to improve safety, quality and efficiency**
- Relying only on cone-beam CT or ultrasound introduces risk of significant human errors. Positioning based on fiducial markers is intuitive for the staff and thereby quicker, easier and safer.

* See ASTRO's white paper on safety for SRS and SBRT: <https://www.astro.org/Patient-Care-and-Research/Clinical-Practice-Statements/Stereotactic-Body-Radiation-Therapy>

** See for example ASTRO's homepage: <https://www.astro.org/Patient-Care-and-Research/Patient-Safety/Safety-is-no-Accident>

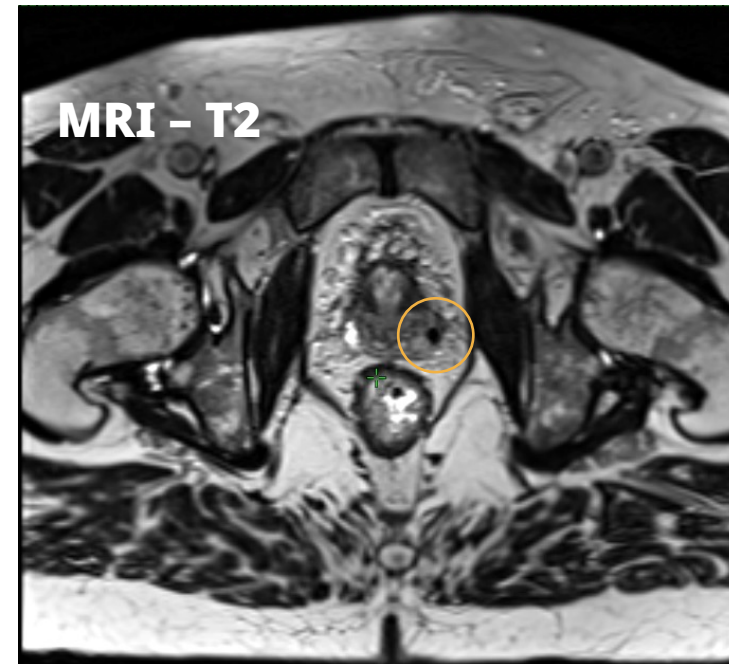
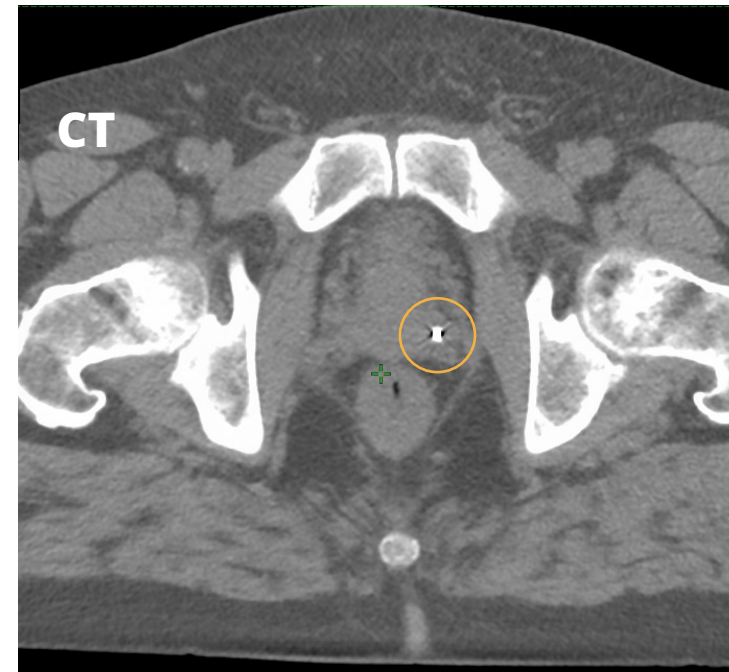
Treatment Planning, CT/MR Fusion

Prior to receiving radiation therapy, patients typically undergo computed tomography (CT) simulation. CT images enables accurate dose calculations in treatment planning systems.

However, due to the superior soft tissue contrast, many patients also undergo Magnetic Resonance Imaging (MRI). Target volume delineation is then typically performed on T2-weighted MR images.

The CT images and MR images needs to be co-registered (fused). Using implanted fiducial markers can make the CT/MRI fusion more reliable and efficient if the fiducial markers can be visualized in both image series.

Gold Anchor fiducial markers has the advantage of being clearly visible on MR images due to the unique and patented marker material. Images to the right showing Gold Anchor 0.4x10 mm MR+ marker implanted in prostate.



During treatment – Patient setup:

The ability to visualize fiducial markers on imaging scans, such as X-rays, CT scans, or MRIs, allows for a more precise alignment of the patient in the same position for each treatment session:

- This reduces the chances of treatment errors and minimizes the risk of delivering radiation to healthy tissue, thus increasing the overall accuracy of the therapy.
- Aligning the patient without fiducial markers introduces risk of significant human errors.
- Positioning based on fiducial markers is intuitive for the staff and thereby quicker, easier and safer.

Read more [here](#)

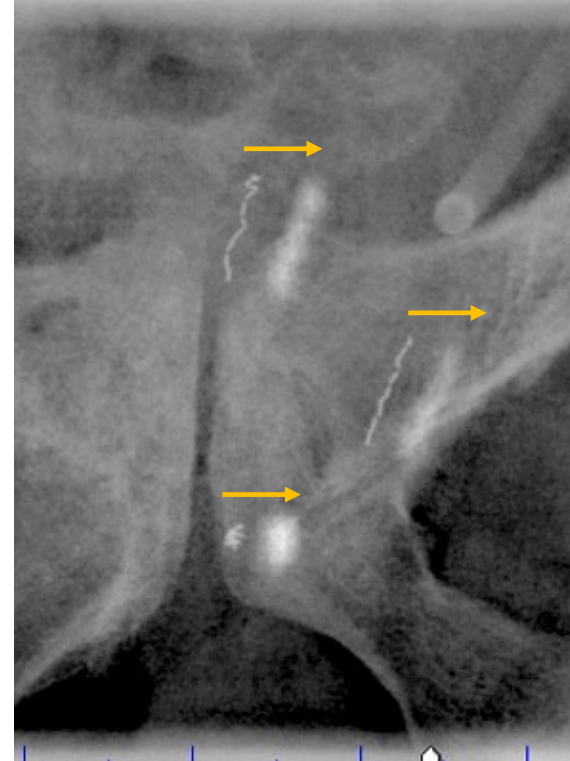
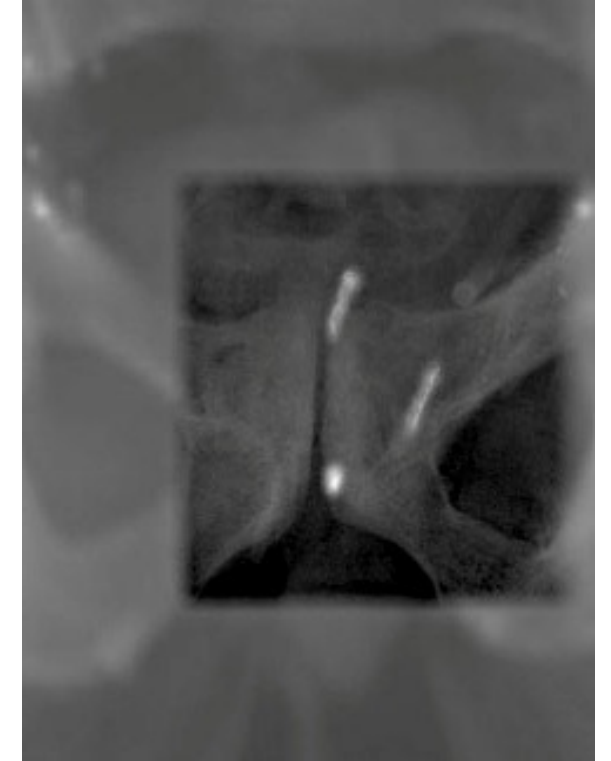
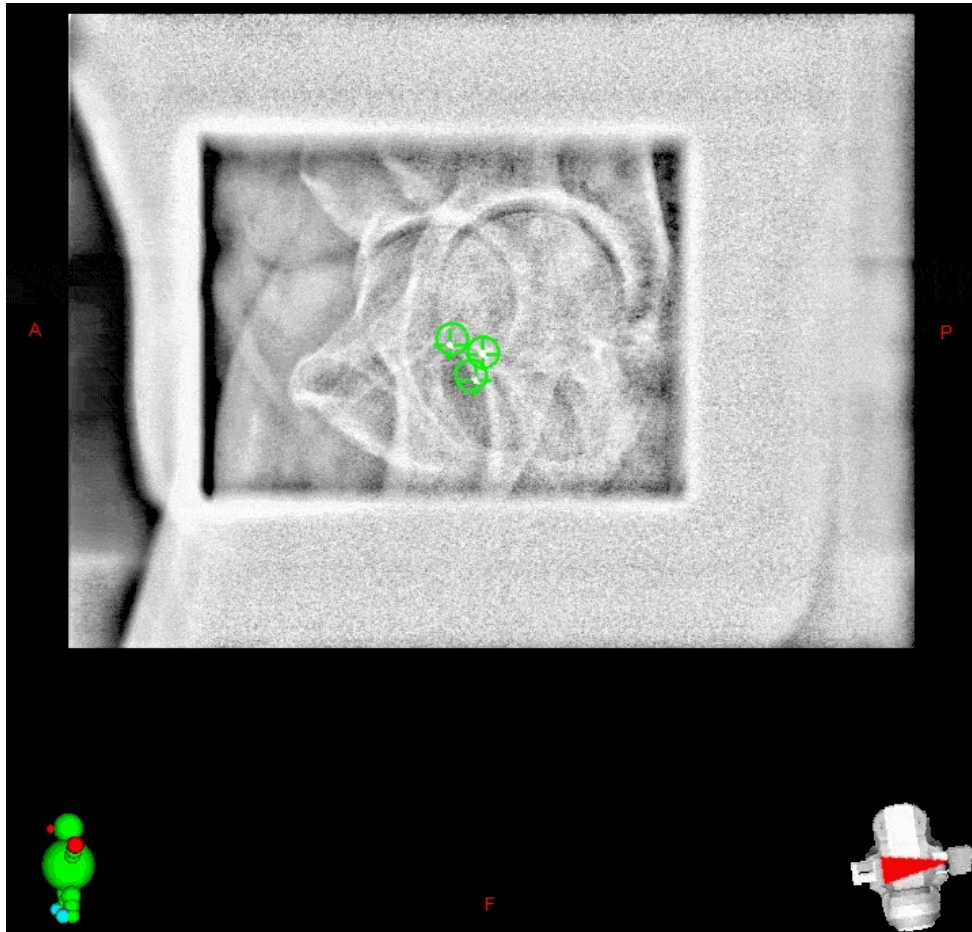


Image above showing overlay of planning image and the daily position image acquired by the linear accelerator. The markers do not overlap so the patient needs to be repositioned.



Now the markers overlap, the patient is correctly positioned and the treatment can start.

During treatment - Real-Time tracking:



Gold Anchor tracked in prostate during treatment with Varian Truebeam Auto Beam-Hold.

Fiducial markers provide clear and consistent reference points for the exact location of the target area. This is particularly important for tumours that might move or shift due to internal bodily processes, such as respiration or digestion.

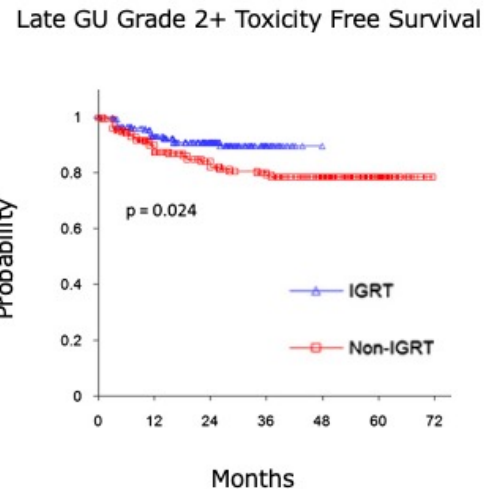
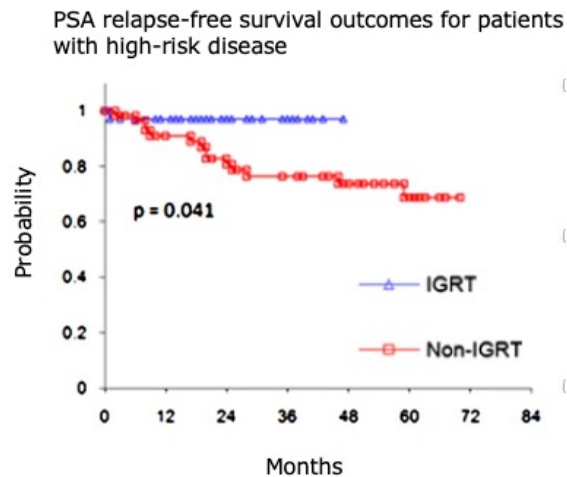
During treatment, imaging techniques can be used to track the position of fiducial markers, ensuring that the tumour remains within the radiation field. This is known as Intrafraction Motion Management. If the markers show any unexpected movement, adjustments can be made to maintain proper targeting, thus increasing treatment precision. There are several systems available for tracking fiducial markers.

Read more [here](#)

Reduced toxicity and improved tumor control with fiducial markers

Using fiducial markers for radiotherapy treatments have proven to not only improve treatment outcomes in terms of reduced side effects (i.e. toxicity) but also in terms of tumour control. One of the most powerful publications proving this claim is from Memorial Sloan Kettering Cancer Center¹. They compared using markers (referred to as “IGRT”) and not using markers (referred to “Non-IGRT”) with the below results.

“Image-guided radiotherapy (IGRT) for prostate cancer with daily target position corrections was associated with a lower rate of late grade 2 or higher urinary toxicities compared with patients who were treated with conventional intensity modulated radiotherapy. In addition, improved prostate specific antigen outcomes were observed for IGRT patients compared with patients treated with non-IGRT among patients with high-risk disease.”



“These data suggest that, for definitive radiotherapy, the placement of fiducial markers and daily tracking of target positioning may represent the preferred mode of external-beam radiotherapy delivery for the treatment of prostate cancer.”

IGRT with fiducial markers is superior to soft-tissue Cone Beam-CT matching

A recent study, with corresponding author from the Icahn School of Medicine at Mount Sinai, compared 2-dimensional kV orthogonal imaging with fiducial markers (kV-FM) and soft-tissue CBCT (ST-CBCT) for IGRT of prostate.

Table 4 Intraobserver variability for test-retest shifts. Mean difference of test-retest shifts ± standard deviation (mm)

	kV-FM	ST-CBCT	t test P-value
A-P	0.4 ± 0.7	2.1 ± 2.2	< .0001
L-R	0.4 ± 1.0	1.3 ± 1.4	< .0001
S-I	0.5 ± 0.7	1.2 ± 1.8	< .0001

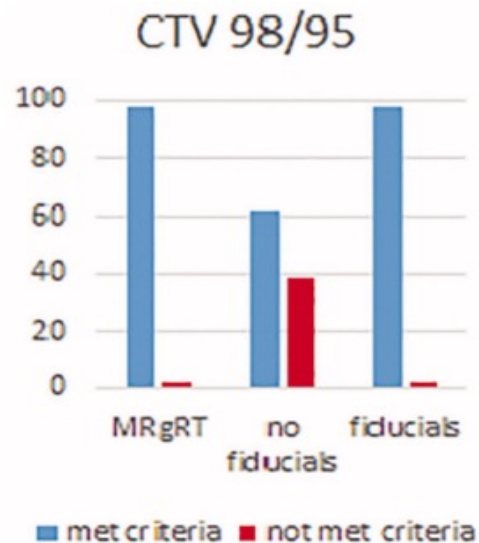
A-P, anterior-posterior; kV-FM, kV orthogonal imaging with fiducial markers; L-R, left-right; S-I, superior-inferior; ST-CBCT, soft-tissue cone beam computed tomography.

They conclude:

“The kV-FM-based daily IG alignment for IMRT of prostate cancer is more precise than ST-CBCT, as assessed by a physician’s ability to reproducibly align images. Given the magnitude of the error introduced by inconsistency in making ST-CBCT alignments, these data support a role for daily kV imaging of FM to enhance the precision of external beam dose delivery to the prostate.”

IGRT with fiducial markers is as accurate as using MR-linac (and obviously much more cost-efficient*)

Authors from the IRCCS Sacro Cuore Don Calabria Hospital in Italy report daily dosimetric variation between MR-guided daily-adaptive RT (MRgRT) and image-guided RT (IGRT) with or without fiducial markers in prostate SBRT.



Results:

“IGRT with fiducials reported high accuracy levels, comparable to MRgRT. MRgRT and IGRT with fiducials reported no significant prostate CTV underdosage, while IGRT without fiducials was associated with occasional cases of prostate CTV under dosage.”

Source: Nicosia L, Sicignano G, Rigo M, et al. Daily dosimetric variation between image-guided volumetric modulated arc radiotherapy and MR-guided daily adaptive radiotherapy for prostate cancer stereotactic body radiotherapy. Acta Oncol., 2021 Feb;60(2):215-22. (<https://doi.org/10.1080/0284186X.2020.1821090>)

*Recent publication from UCLA affirms this claim: Parikh NR, Clark MA, Patel P, Kafka-Peterson K, Zaide L, Ma TM, Steinberg ML, Cao M, Raldow AC, Lamb J, Kishan AU. Time-Driven Activity-Based Costing of CT-Guided vs MR-Guided Prostate SBRT. Appl Radiat Oncol. 2021 Sep;10(3):33-40. (<https://doi.org/10.1200/JOP.19.00605>)

“In conclusion, the base-case of this TDABC analysis estimates \$1,497 in increased direct costs utilized by delivering prostate SBRT with MRgRT instead of CTgRT”

Gold Anchor enables a superior IGRT solution for prostate SBRT

IGRT is standard of care for hypofractionation of the prostate. There are however several ways to perform IGRT and below is a comparison illustrating downsides with other options than Gold Anchor.

	High target dose coverage	Low invasiveness	Resource efficiency
IGRT with Gold Anchor	✓	✓	✓
IGRT with traditional fiducials	✓	✗	✓
CBCT without fiducials	✗	✓	✓
MR-guided daily-adaptive RT	✓	✓	✗

Many prostate SBRT-trials strongly recommend or require fiducials

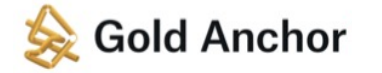
Study	# of patients	Fiducial markers used?
>> HYPO-RT-PC	n = 1200	<u>Required</u>
>> PACE	n = 858	<u>Strongly recommended</u>
>> HEAT	n = 456	<u>Required</u>
>> NINJA	n = 472	<u>Required</u>

Extract from the PACE¹ trial:

“Before radiotherapy, three or more prostatic fiducial markers were strongly recommended for all participants to permit more accurate image-guided radiotherapy and CT or MRI fusion. ..A radiotherapy planning MRI scan was strongly recommended to be fused to the CT scan (preferably by fiducial match) for improved prostate anatomical definition.”

1) Brand DH, Tree AC, Ostler P, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. Lancet Oncol 2019;20:1531-43. DOI: [https://doi.org/10.1016/S1470-2045\(19\)30569-8](https://doi.org/10.1016/S1470-2045(19)30569-8)

Gold Anchor is a fiducial marker with unique features and benefits.



Minimally invasive

Industry leading thin needles

Great visibility

Also on MRI, thanks to unique material

Instant stability

Multiple cut-outs allow the marker to fold