SBRT FOR LOCALIZED PROSTATE CANCER: BIOLOGY MEETS TECHNOLOGY

Over the past decades, tremendous advances in radiotherapy technology have enabled improved precision in radiation therapy: Image guidance, high-precision dose delivery and accurate target definition enable safe dose escalation, potentially resulting in improved tumour control and decreased treatment-related morbidity.

In prostate cancer, these technological developments progressed at the same pace as the increased understanding of the biological mechanisms underlying the use of hypofractionation: as the α/β of prostate cancer is lower than that of the majority of human tumours, close to a value that is characteristic of late responding tissues, the delivery of fewer and larger fractions than used in conventional radiotherapy, might effectively improve the therapeutic ratio while shortening the overall treatment time.

Shorter radiation schedules substantially decrease patients' distress especially in the elderly population, due to the high number of radiotherapy department visits usually associated with conventional fractionation. As such, hypofractionated radiotherapy can be implemented without compromising treatment efficacy and increasing patient compliance as well. Mature results from non-inferiority trials [1-4] have confirmed that moderate hypofractionation (2.4–4 Gy daily fractions) is noninferior to conventional fractionation, thus leading to the widespread adoption of this hypofractionation regimen for localized prostate cancer. The sensitivity of prostate cancer to increased fraction sizes have provided the basis to extend the treatment to considerably larger fractions of 6.7–10 Gy. This strategy, widely known as SBRT, is emulating the high-dose-rate (HDR) brachytherapy hypofractionated approach in a noninvasive and more convenient fashion, enabling steep dose gradients without the need for hospitalization and catheterization, the discomfort of keeping delivery needles inserted for an extended time period (in the case of low-dose-rate (LDR) implants) or the need of managing the pain resulting from the indwelling transperineal HDR catheters.

In the last years, evidence from several phase I-II has shown excellent early biochemical outcomes and acceptably low toxicity rates predominantly in patients with low-risk or intermediate-risk prostate cancer, but prevented any definitive conclusion regarding the clinical benefits of extreme hypofractionation. Recently, a randomised, phase 3 non-inferiority trial [5] showed that ultra-hypofractionated radiotherapy is non-inferior to conventionally fractionated radiotherapy for intermediate-to-high risk prostate cancer regarding failure-free survival, after a median follow up of 5 years. Furthermore, in a multi-institutional study [6] patients were randomized to 2 ultra-hypofractionated radiation schedules involving 5 to 12 fractions: after a median follow up of 3.8 years, the bowel, urinary, and sexual patient-reported outcomes (PROs) were comparable to those for standard (38 to 44 fractions) regimens. Taken together, these findings pave the way for a broader dissemination of SBRT for localized prostate cancer.

When hypofractionated radiotherapy is delivered via SBRT (high dose per fraction, few fractions, high dose gradient) a strict adherence to dose volume constraints to the surrounding at-risk organs is paramount. Specifically, the steep dose gradients of SBRT plans require a high level of reliability during the entire treatment delivery process. At even small distances from the target the radiation dose decreases rapidly; hence, prostate motion during treatment might result in spatial misses and unacceptable exposure to radiation of surrounding healthy tissues. Thus, intrafraction tracking must be employed, for example, using implanted radiopaque fiducial markers and electromagnetic beacon transponder technology. Unlike other types of fiducial markers that need to be localized using X-rays (increasing the ionizing radiation exposure), the electromagnetic transponder technology is particularly suited for organs that have a tendency to change in shape by providing objective location coordinates with the added benefit of tracking the tumour in real-time throughout the entire treatment delivery period. This accurate targeting is crucial when high radiation doses are delivered rapidly, for example when using fast flattening-filter-free beam radiation.

RayPilot® system with RayPilot HypoCath® (Image 1) is a removable electromagnetic tracking device

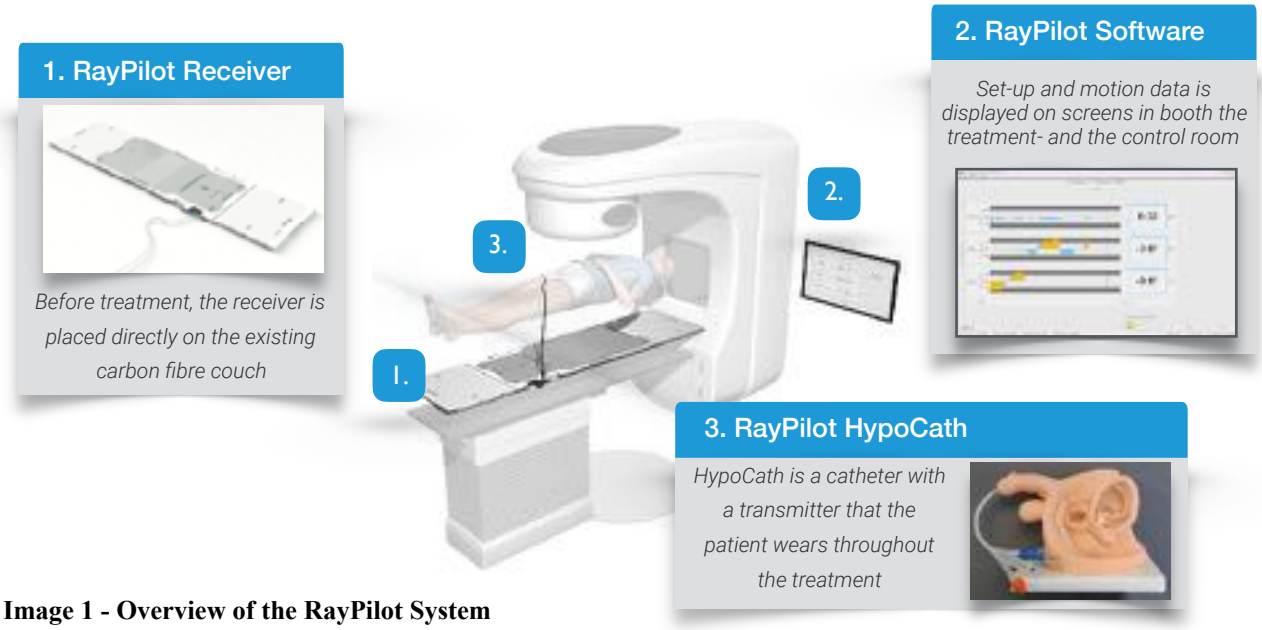

Image 1 - Overview of the RayPilot System

for prostate and urethra localization and monitoring during prostate cancer SBRT. RayPilot HypoCath is integrated in a standard urinary catheter (Foley), thus eliminating the need of a surgical intervention with less risk and increased convenience for the patient who can benefit from non invasive continuous non-ionizing real time tracking of the prostate during treatment. Furthermore, the final catheter removal allows an MRI artifact-free follow-up. Such careful measure to minimize treatment related toxicities has been implemented in the first patient in the world treated at the University of Milan Bicocca - Ospedale San Gerardo, confirming that this strategy allows to fulfill strict planning criteria keeping the average target motion within 2 mm during the beam delivery without compromising patient's comfort and compliance. To date 4 patients have been treated using RayPilot system with RayPilot HypoCath and the transmitter shifts are reported in Table 1.

Further fine-tuning of the workflow procedure on a larger scale may result in an improved accuracy with the potential for further reduction in the number of treatment sessions (potentially limiting the treatment to a single event), making SBRT well positioned to rapidly become the procedure of choice for the management of all patients with localized prostate cancer, especially in light of the increasing number of elderly patients in need for treatment.

Table 1 – RF transmitter shifts registered in the 4 patients treated at University of Milan Bicocca - Ospedale San Gerardo.

	Lateral (mm)	Longitudinal (mm)	Vertical (mm)
1st patient			
Range	[-0.6, 0.9]	[-2.0, 1.8]	[-2.8, -0.5]
Average ± std dev	0.1 ± 0.1	-0.4 ± 0.6	-1.3 ± 0.2
2nd patient			
Range	[-1.3, 0.9]	[-2.3, 5.2]	[-3.1, 4.4]
Average ± std dev	-0.3 ± 0.3	-0.6 ± 0.7	-0.6 ± 0.6
3rd patient			
Range	[-0.2, 1.0]	[-1.6, 0.9]	[-2.0, 0.6]
Average ± std dev	0.3 ± 0.1	-0.4 ± 0.2	-0.8 ± 0.2
4th patient			
Range	[-2.1, 0.4]	[-3.3, 2.7]	[-2.8, 0.5]
Average ± std dev	-0.5 ± 0.3	0.1 ± 0.4	-1.0 ± 0.4

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