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Short Communication

Single fraction urethra-sparing prostate cancer SBRT: Phase I results of the ONE SHOT trial

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ABSTRACT

The ONE SHOT trial is the first phase I/II prospective, multicenter, single-arm study assessing the efficacy and safety of a single-dose SBRT for men with localized prostate cancer. Aim of this paper is to present the phase I results of a 19 Gy single fraction urethra-sparing SBRT with real-time electromagnetic tracking.

Randomized clinical trials have shown that moderate hypofractionated radiotherapy (RT) (*i.e.* 2.5–4 Gy per fraction) has become a valid alternative to conventionally fractionated RT in patients with prostate cancer (PCa) [1–3]. The rationale of hypofractionation is based on the strong radiobiological evidence of the low α/β ratio of PCa cells ($\sim$1.5 Gy) and the greater sensitivity to high dose per fraction [4].

Extreme hypofractionation (>6 Gy per fraction) delivered with stereotactic body radiation therapy (SBRT) in 4 to 5 fractions has become in the last years an alternative treatment strategy for localized PCa with promising results in terms of disease control and toxicity [5,6], not inferior to conventionally fractionated RT [7]. Whether treatment fractions can be further reduced with SBRT is therefore an appealing research matter yet to be explored. Several authors have demonstrated the feasibility of single fraction treatments with high dose rate brachytherapy (HDR-BT), even if long-term results, despite a low rate of radiation-induced toxicity, were quite disappointing in terms of local control [8,9]. Applicability of the linear quadratic (LQ) model at high doses per fraction remains however somewhat uncertain, especially using HDR-BT [10].

To address the role of single fraction stereotactic body radiation therapy (SBRT) in prostate cancer, a phase I/II prospective, multicenter, single-arm study, the ONE SHOT trial [11], was designed to evaluate the efficacy and safety of this monotherapy treatment. The aim of this report is to present the phase I results of a 19 Gy single fraction urethra-sparing SBRT with real-time electromagnetic image guided RT (IGRT) tracking for localized PCa.

Materials and methods

Seven patients with localized PCa from two among the five participating institutions were enrolled in the phase I study between August 2017 and December 2018 (Clinicaltrials.gov identifier: NCT03294889) [11]. One patient was excluded from the trial for an acute prostatitis following the implantation of the beacons into the prostate leaving a total of 6 patients for the intention-to-treat analysis.

Disease characteristics were as follows: low- or intermediate-risk localized PCa (cT1c-2c N0 M0; Gleason $\leq 3+4$; PSA ≤ 15 ng/ml; mpMRI-based prostate volume $\leq$70 cc; absence of significance tumor in the transitional zone and no extracapsular extension on mpMRI). Additional inclusion criteria were: age between 18–85 years, WHO performance status 0–1, and International Prostate Symptoms Score (IPSS) < 10 (alpha blocker allowed). Exclusion

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criteria included: prior pelvic RT, previous surgery for prostate cancer, previous or ongoing androgen deprivation therapy, hip prosthesis, and/or transurethral resection <12 weeks before registration.

All six patients were treated with a single SBRT fraction of 19 Gy to the whole prostate gland with the 2/3 of the proximal seminal vesicles included in 4 patients with a Roach score ≥15%, using a *TrueBeam*® linear accelerator (Varian, Palo Alto, US) with a volumetric modulated arc therapy (VMAT) technique. Intra-fractional motion was monitored with 3 intraprostatic electromagnetic transponders (*Calypso*® localization system, Varian, Palo Alto, US), with a threshold limit of ±3 mm and rotation of 10° using the IGRT procedure previously described [11]. Prostate Planning Target Volume (PTV) was defined as Clinical Target Volume (CTV) + 5 mm isotropic expansion in all directions except for a 3 mm margin posteriorly towards the rectal wall. A urethra-sparing technique was used by prescribing a dose of 17 Gy to the prostatic urethra (defined inserting a 12 French Foley catheter during simulation and treatment) with a 2 mm margin urethra planning risk volume (PRV). Organs at risk (OAR) contouring was performed according to RTOG guidelines [12]. Definition of volumes and dose reporting were in accordance with International Commission on Radiation Units and Measurements (ICRU) report 83, assessing dose variations in the PTV with the near-minimum (D98%) and near-maximum (D2%) doses and using dose constraints as previously described [11].

Genito-urinary (GU) and gastro-intestinal (GI) toxicities were evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) classification v4.03 at baseline, at five days (D5) after SBRT, and at six and twelve weeks (W6; W12). IPSS [13], IIEF-5 (International Index of Erectile Function) [14], and Quality of Life (QoL) score performed with EPIC questionnaire (Expanded Prostate Cancer Index Composite) were also used [15]®.

The primary endpoint of phase I was safety, assessed by the occurrence of Grade ≥3 acute adverse events (AE) following the single fraction SBRT during the first 3 months in a "3+3"cohort-base. Efficacy will be evaluated as primary endpoint of the phase II trial using biochemical relapse-free survival (bRFS) at 3 years in 39 additional patients (45 patients total), according to the RTOG-ASTRO recommendations (Phoenix Consensus Conference) [16]. Secondary endpoints of phase II will be occurrence of acute and late AE, progression-free survival (PFS), prostate cancer-specific survival (PCSS), overall survival (OS) rates and QoL.

Results

Among the 6 patients included and treated in the trial, median age at SBRT was 75 years old (range, 67–82 years) with a median pre-treatment PSA of 8.1 ng/ml (range, 3.9–10.8 ng/ml). Clinical T-stage was T1c, T2a and T2b in 3, 2, and 1 patient, respectively, with a Gleason score of 3+3 and 3+4 found in 2 and 4 patients, respectively. All patients presented an intraprostatic disease

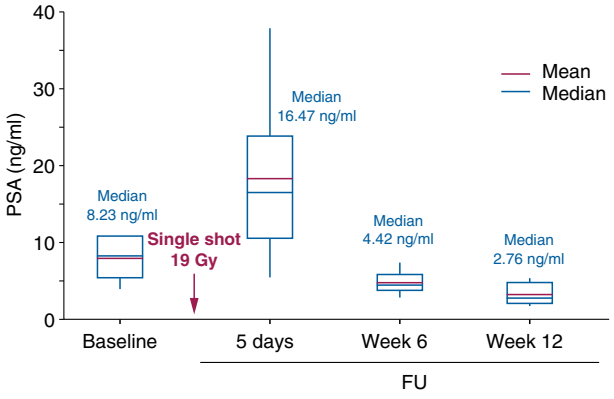

Fig. 1.

classified on mpMRI as T2a, T2b and T2c in 2, 3 and 1 patient, respectively.

All six patients completed the treatment according to the protocol by respecting all dose constraints as assessed by the prospective RTQA evaluation, without protocol deviations. The mean beam on time and overall treatment time (interval time between the delivery of the 1st and the last monitor unit) was 4.4 and 14.1 minutes, respectively. No acute toxicity ≥ grade 3 was reported during the three-month follow-up without activation of the stopping rule. Table 1 describes the occurrence of GU and GI toxicity during the acute phase. The most frequent adverse event observed was grade1-2 GU toxicity (urgency and frequency, i.e., 50% of Grade 2 at D5), which resolved on W6 (33% of grade 2 at W12). No grade 2 GI events were reported during the follow-up with only 17% of grade 1 rectal toxicity reported at W12.

As illustrated in Fig. 1A, IPSS increased from baseline to D5 and W6 (mean, from 3.5 (SD ± 2.9) to 13.2 (SD ± 8.5) and 16.2 (SD ± 7.9), respectively) decreasing progressively at W12 (mean, 8.8; SD ± 4.5). The EPIC urinary domain mean score was 92 pre-treatment (SD ± 5.4), 73 (SD ± 19.3) at D5, 79 (SD ± 17.5) at W6, and 87 (SD ± 9.3) at W12, while the EPIC bowel domain mean score remained stable over time (95 (SD ± 4.4), 91 (SD ± 19.8), 85 (SD ± 26.1), and 90 (SD ± 13.1), respectively, at the four time points). No impact of SBRT was observed on IIEF-25 scores and the EPIC sexual domain. The mean IIEF-25 score was 10.2 (SD ± 6.4) at baseline and 9.0 (SD ± 7.1) at W12, while the mean EPIC sexual score values were 46.3 (SD ± 25) and 44.5 (SD ± 17.7) at the same time points. PSA values bounced at D5 (median, from 8.2 to 16.5 ng/ml) decreasing successively up to a value of 2.8 ng/ml at W12 (Fig. 1B).

Discussion

To our knowledge, ONE SHOT is the first multicenter phase I/II study evaluating safety and efficacy of a single fraction SBRT treatment for men with localized PCa. Here we report the phase I results

Table 1
Gastrointestinal and genitourinary acute toxicities (first 3 months).

	Baseline	After SBRT – Day 1	Week 1 – Day 5	Week 6	Week 12
Gastrointestinal toxicity					
Grade 0	5 (83.3%)	6 (100.0%)	6 (100.0%)	4 (66.7%)	5 (83.3%)
Grade 1	1 (16.7%)	0 (0.0%)	0 (0.0%)	2 (33.3%)	1 (16.7%)
Genitourinary toxicity					
Grade 0	2 (33.3%)	2 (33.3%)	0 (0.0%)	0 (0.0%)	2 (33.3%)
Grade 1	2 (33.3%)	1 (16.7%)	3 (50.0%)	5 (83.3%)	2 (33.3%)
Grade 2	2 (33.3%)	3 (50.0%)	3 (50.0%)	1 (16.7%)	2 (33.3%)

of the first 6 patients recruited and treated according to the study protocol. Primary endpoint of safety was reached; during the first 3 months of follow-up no grade $\geq$ 3 acute toxicities were observed. Our preliminary results indicate a promising profile of both acute GU and GI toxicities. The incidence of grade 1–2 GU toxicities was 50% at D5, decreasing to baseline at W12. None of the patients experienced grade 2 GI adverse events; 33% of the patients presented grade 1 rectal toxicity at W6, resolved at W12.

The question of the long-term efficacy of a single high dose irradiation of 19 Gy remains open. The radiobiological rationale of a single fraction is sustained by biologically equivalent dose (EQD) calculations based on the LQ model, even though its reliability for doses per fraction above 7 Gy has been challenged [17]. Using a α/β ratio 1.5 Gy, 19 Gy as a single fraction would deliver a biological equivalent dose similar to 40 Gy in 5 fractions of 8 Gy ($EQD_{2Gy}$of 111.3 and 108.5 Gy, respectively), an ablative SBRT schedule commonly used to treat PCa [18]. Assessing the possibility to treat PCa with a single and unique fraction of high dose irradiation remains therefore a challenging research subject.

Prostate single dose monotherapy has been explored in the last years by several authors using HDR-BT. Despite favorable preliminary results [19–21], long-term disease control remains disappointing with a 6-year bRFS of 66% in the series of Prada et al. [8] and 77.2 % at 5-years in the series by Siddiqui et al. [9]. Recently, Tharmalingam et al., presented the results of a 19 Gy single fraction HDR-BT trial at the European Society for Radiotherapy and Oncology (ESTRO 38) meeting; the largest series presented so far, included 441 patients with localized PCa and while the 3-year bRFS rate was 100% for low-risk patients, in intermediate- and high-risk patients the bRFS rates at 3-year dropped to 86% and 57%, respectively [22]. Noteworthy, relapses after 19 Gy HDR-BT monotherapy are mainly intraprostatic, predominantly associated with the site of initial disease [23].

How HDR-BT monotherapy findings overturning the LQ estimations for PCa can be applied to SBRT remains, however, a pending question. Uncertainties in disease control rates prediction by the LQ model with HDR-BT have been reported by Roberts et al., especially at higher doses [10]. In a retrospective series of 3145 PCa patients among 10 different institutions treated with HDR-BT alone or combined with EBRT, tumor control rates were lower than expected from LQ projections when HDR-BT dose were higher than 30 Gy, when doses per fraction were 9–15 Gy and the treatment was completed in only 1 week. Furthermore, SBRT schedules of 5×7.25 Gy ($EQD2_{Gy}$90 Gy) gave a bRFS of 95% at 5-years [6], substantially the same as monotherapy fractionated HDR-BT series, where EQD_{2Gy} was comparatively much higher [24–26]. Although caution is recommended, only prospective controlled studies like the ONE SHOT trial will be able therefore to properly address the impact of single fraction 19 Gy SBRT in prostate cancer outcomes.

One of the strengths of the present study is the homogeneity of the treatment technique employed. Indeed, participation to the trial was restricted to *TrueBeam®-Calypso®* users within Europe with experience in using such technology for PCa SBRT. Irradiation was always implemented with two arcs of a VMAT technique with an overall treatment time of less than 15 minutes. A centralized QA program assessed for potential deviations in the treatment protocol from dosimetry to treatment delivery.

Conclusions

Nineteen Gy single-fraction SBRT irradiation of the whole prostate with urethra sparing to 17 Gy was feasible and well tolerated. Long-term results of phase II ONE SHOT trial will certainly shed light on the efficacy and safety of a single-dose SBRT monotherapy in the exclusive treatment of localized PCa.

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