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BIT-ART: Multicentric Comparison of HDR-brachytherapy, Intensity-modulated Radiotherapy and Tomotherapy for Advanced Radiotherapy in Prostate Cancer

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Abstract. *Background/Aim: The aim of the study was to evaluate acute and late genitourinary (GU) and gastrointestinal (GI) toxicity in patients with high- or intermediate-risk prostate cancer. Patients and Methods: We evaluated data of patients from three Radiation Oncology Departments (Rome, Lübeck and Perugia). Patients treated in Rome underwent exclusive intensity-modulated-radiotherapy (IMRT) or IMRT plus high-dose-rate interventional radiotherapy (HDR-IRT). IMRT plus two fractions HDR-IRT was performed in Lübeck, while in Perugia Helical Tomotherapy was performed. The Common Toxicity Criteria for Adverse Event (Version 4.03) scale was used to describe acute and late toxicity. Results: At a median follow-up of 28 months, all 51 patients were alive and disease-free. Patients treated by HDR-IRT plus VMAT showed only G1-2 genitourinary- gastrointestinal (GU-GI) acute and late toxicity. Univariate analysis showed a lower risk of acute GU toxicity (p=0.048) in IMRT+HDR-IRT. Conclusion: Low grade and less acute GU toxicity was observed in patients undergoing HDR-IRT boost.*

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Prostate cancer is a common disease, accounting for an estimated 19% of men malignancies and 9% of male cancer deaths (1). Prostate cancer radiotherapy is delivered by external beam radiotherapy (EBRT) or brachytherapy (interventional radiotherapy, IRT, BT) as a monotherapy or as a combination of both procedures.

Local biochemical relapse continues to represent the main pattern of failure after standard treatment approaches and dose-escalation as a means of treatment intensification to improve biochemical and survival outcomes (2). Despite IRT plays an important role in the treatment of localized low-risk prostate cancer, it is not largely used (3, 4).

For intermediate- and high-risk disease, the best treatment of prostate cancer has not yet been defined, due to lack of well-designed randomized trials comparing different treatment modalities (4).

High-dose-rate (HDR) IRT has been shown to be associated with high radiation dose conformity within the target volume, rapid dose fall-off in adjacent organs at risk, relatively short treatment time, and excellent cosmetic and good functional outcomes (5-8).

The major advantage of HDR IRT, compared with external beam radiotherapy (EBRT), is its ability to overcome the organ motion and to spare the organs at risk (OARs), as well as the potential of biological planning (9-17). IRT as a boost in combination with EBRT may be the optimal solution in locally advanced cases since IRT alone may not adequately treat the peri-prostatic tissue (15, 18). Case series and randomized trials have shown that HDR boost complementary to external beam treatment provided good

Table I. *Patients features. Total number of patients (n°): 51.*

Median age (years)	74			
	Total	Lübeck	Rome	Perugia
Stage (n°)				
cT1c	1	1	0	0
cT2a	1	0	1	0
cT2b	10	4	0	6
cT2c	17	3	3	11
cT3a	10	0	10	0
cT3b	12	1	11	0
GS (n°)				
<7		0	10	5
>7		9	15	11
NK		0	0	1
Baseline PSA Value (n°)				
<10 ng/ml		5	16	2
>10 ng/ml and <20 ng/ml		2	7	2
>20 ng/ml		2	2	13
Risk features (n°)				
Intermediate - Risk	28	6	5	17
High - Risk	23	3	20	0
Basal uroflowmetry (n°)				
Regular	17	5	5	7
Reduction	33	4	20	9
Pathological	1	0	0	1
ADT (n°)				
Pre-RT	40	5	25	10
Only During-RT	11	4	0	7

ADT: Anti-androgen treatment; RT: radiotherapy.

Table II. *Treatment characteristics.*

Technique	Institution	Dose HDR-IRT	Dose EBRT (IMRT or HT)	EqD2 total prostate dose
HDR Boost +IMRT	Rome Lübeck	15 Gy in 1 fr 30 Gy in 2 fr	46 Gy in 23 fr 50 Gy in 25	100 Gy 158 Gy
HT alone	Perugia	0	74.25 Gy in 33 fr Or 67.50 Gy in 25 fr	79,55-81 Gy
IMRT alone	Rome	0	80 Gy in 40 fr	80 Gy

HDR-IRT: High-dose-rate interventional radiotherapy; EBRT: external beam radiotherapy; IMRT: intensity-modulated-radiotherapy; HT: helical tomotherapy; EqD2: equivalent dose to 2Gy/fraction dose.

results in terms of local control and survival (16, 18-22) such as in reduction of biochemical failure (18, 23).

In this multicentric study, we evaluated different treatment techniques with special focus on acute and late genitourinary (GU) and gastrointestinal (GI) toxicity outcomes in patients with prostate cancer treated by HDR-IRT plus intensity-modulated-radiotherapy (IMRT), comparing to patients treated by exclusive helical tomotherapy (HT) or exclusive IMRT.

Patients and Methods

The present comparative study consisted of three cohorts from three European radiation oncology departments (Rome, Lübeck and Perugia), to evaluate acute and late GU and GI toxicity after different kinds of dose escalation radiation therapy treatments.

Inclusion criteria. Selection criteria for this analysis were high-risk features (Stage T3 or Gleason Score >7 and/or prostate specific-antigen level >20 ng/ml) or intermediate-risk features (Stage T2b/c and GS >7 and/PSA >10 ng/ml and <20 ng/ml), and no metastatic disease (cM0) (24). For patients who underwent HDR-IRT boost additional selection criteria were identified: no trans-urethral resection of the prostate (TURP) in the previous sixth months and no anesthesiologic contraindications. Table I reports demographic and clinical features of patients.

Work-up. In all institutions, pre-treatment work-up included magnetic resonance (MRI) staging, clinical evaluation, basal uroflowmetry, testosterone and initial PSA evaluation (3, 25-27). No patients underwent surgery. Local recurrence was detected by multi-parametric magnetic MRI (mpMRI) or MRI with endorectal coil and choline positron emission tomography-computed tomography (PET-CT) or CT scans when post-treatment PSA levels exceeded 1 ng/ml. A total of 49 patients (96%) received androgen deprivation therapy (ADT) (26, 28).

Protocols. Patients treated in Rome at Gemelli ART (Advanced Radiation Therapy) Department - IOC (Interventional Oncology Center) underwent IRT alone or IRT complementary to IMRT. Exclusive IMRT was performed in 40 daily fractions for a total dose of 80 Gy to whole prostate and 72 Gy delivered to seminal vesicles or seminal vesicles' bases, according tumor stage. Combined EBRT+IRT treatment was performed with one fraction of HDR. The total dose was 15 Gy on the high-risk zone (peripheral zone) during a one- or two-nights hospitalization. Under spinal anesthesia, an intraoperative pre-planning was performed, in order to identify the optimal implant geometry. The definitive Trans-Rectal Ultra Sound (TRUS)-based treatment planning was realized after completing the implant in the bunker. Two weeks after IRT, all patients received EBRT (46 Gy in 23 daily fractions), by IMRT resulting in EQD2 100 Gy total dose (assessing prostate alpha/beta α/β ratio at 1.5) (29) and a total treatment time of 8 weeks.

Patients treated in Lubeck underwent two fractions of HDR-BT, the total dose per fraction was 15 Gy plus IMRT 50 Gy, resulting in a total nominal dose of 80 Gy (EQD2 158 Gy) in six weeks total treatment time. Real time biological (mpTRUS) online planning based focal dose escalation was practiced.

In Perugia, HT treatment was performed. The total dose delivered to whole prostate was 74.25 Gy in 33 daily fractions or 67.50 Gy in 25 daily fractions (EQD2 79.55-81 Gy) and 62 Gy or 56.25 Gy delivered to seminal vesicles. The treatment characteristics are reported in Table II.

Clinic visits occurred every 4 months for the first year, every 6 months for the next 4 years and annually thereafter. Acute and late toxicity were reported according to the Common Toxicity Criteria

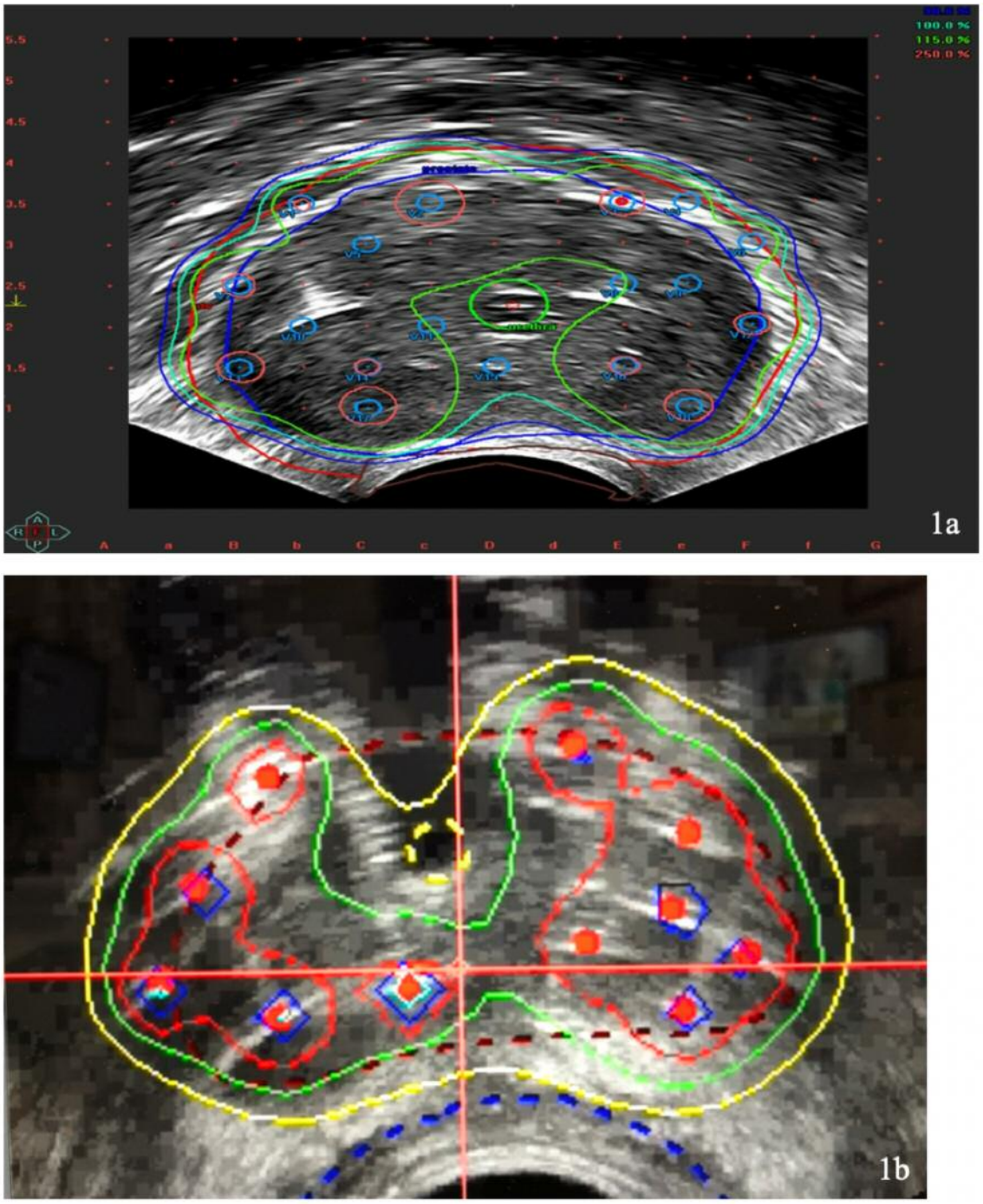

Figure 1. *Dose distribution of HDR-IRT (Rome 1a) and biological planning (Luebeck 1b). Axial views show high conformality of HDR-IRT. a) Isodose lines: Cyan 15.0 Gy – Green 17.25 Gy – Red 37.5 Gy. b) Isodose lines: Yellow 7.5 Gy – Green 10.00 Gy – Red 15.0 Gy – Blue 30.0 Gy.*

for Adverse Event (CTCAE Version 4.03) by the National Cancer Institute (30).

Statistical analysis. Prognostic factors *i.e*. age (≤75 years old *vs*. >75 years old), class of risk (intermediate risk *vs* high risk), ADT (yes *vs*. no), RT techniques (HT *vs*. VMAT *vs*. VMAT+BT) and uroflowmetry parameters (regular *vs* pathological parameters) were analyzed using descriptive statistics.

Categorical data were analysed by the chi-square or Fisher exact test. Two-tailed $p<0.05$ was considered significant. All calculations were performed with IBM-SPSS®, version 25.0, (IBM Corp., Armonk, NY, USA).

Results

Data of fifty-one patients (23 with intermediate-risk and 28 with high-risk features) treated from July 2013 to August 2016 were evaluated.

EBRT treatment was performed in 34 patients, of whom 17 patients were treated by hypofractionated HT in Perugia and 17 patients underwent exclusive EBRT treatment with IMRT technique in Rome. HDR- IRT boost was performed in 17 patients, 8 in Rome and 9 in Lübeck (Table II). Three examples of dose distribution of HDR-BT (Figure 1A and B), HT (Figure 2) and IMRT (Figure 3A and B) are reported. Forty patients (78%) received neo-adjuvant, concomitant and adjuvant ADT; 11 patients (22%) received only adjuvant ADT.

Reduced uroflowmetry parameters before treatment were observed in 32/51 patients (62%).

The mean follow-up (FU) time of the entire cohort was 28 months (range=6-50 months). All patients are alive. None had local or biochemical recurrence.

Grade 1-2 acute GU toxicity occurred in 7 patients treated by combined HDR boost and IMRT, 10 patients treated by IMRT alone, and 11 patients treated by HT. Grade 1-2 acute GI toxicity was observed in 4 patients treated by combined IRT+IMRT, 6 patients treated by HT and 8 patients treated by IMRT.

No GU Late Grade 2-3-4 toxicities were reported; GU G1 toxicity was observed in two patients treated by combined technique (IRT+IMRT) and in one patient treated by exclusive IMRT.

One patient treated by IMRT alone showed G1 GI late toxicity; no G2-3 GI late toxicity was observed (Table III).

Univariate analysis indicated a lower risk of acute GU toxicity by the use of IMRT+IRT (p=0.048).

None of the other analyzed factors (age, class of risk) showed a significant impact on toxicities outcomes.

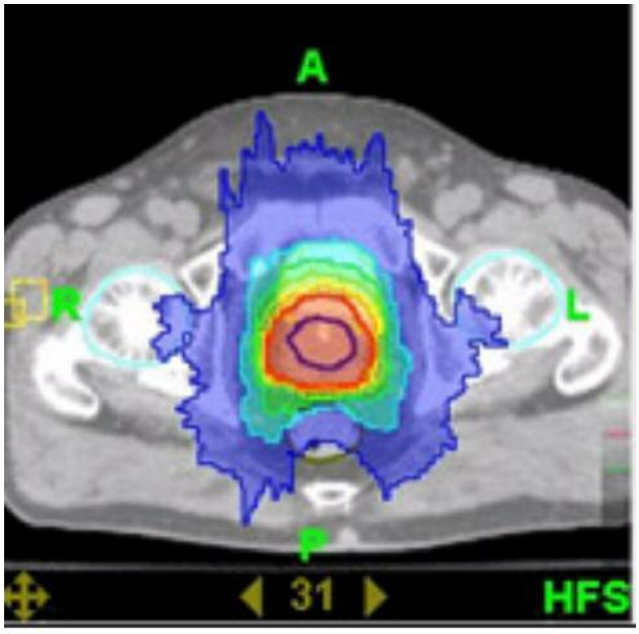

Figure 2. *Dose distribution of helical tomotherapy (HT). Axial views show dose distribution relative to HT planning target volumes (PTVs) and organs at risk (Perugia).*

Discussion

In prostate cancer, biochemical relapse still represents the main site of failure after standard treatment approaches and dose-escalation as a means of treatment intensification improves biochemical and survival outcomes.

This study was designed to be a preliminary hypothesis generating analysis, investigating the feasibility of combined dose-escalation treatment approaches (EBRT alone *versus* EBRT combined with a boost of HDR-IRT, including biological planning at IRT) in intermediate- and high-risk localized prostate cancer patients evaluating toxicities outcomes.

Some previous retrospective analyses or randomized trials have compared outcomes in conventionally fractionated or hypo-fractionated EBRT as monotherapy with treatments including an IRT boost.

The literature data (13, 15, 16) has reported a statistically significant benefit in terms of biochemical disease-free survival in favor of the EBRT combined with BT.

Furthermore, in several investigations focal dose escalation based on biological imaging was found practical in reducing dose on OARs and non-dominant prostate target volumes (31-35). The existing high level of evidence (Level I, Group 1) presenting the superiority of HDR brachytherapy boost complementary to external beam boost (11) raised the question if mpTRUS is eligible for intraprocedural definition of relevant dominant (high Gleason) subvolumes within the prostate. Controlled investigations stated the equality of mpTRUS with mpMRI (36, 37); however, prospective randomized clinical trials are needed in the future.

In the presented analysis of different kind of dose escalation (EQD2: 79-158 Gy) treatments, we observed an advantage, in terms of acute GU toxicity outcomes, of the combination EBRT+IRT independently from the EBRT fractionation as only Grade 1-2 acute GU toxicity occurred.

Toxicity outcomes and quality of life (QoL) scores in patients undergoing HDR-IRT boost in prostate cancer has widely been assessed (13, 16, 18, 19, 21, 25). Hoskin *et al.* (15) randomized 220 patients to receive either hypofractionated EBRT alone or combined hypofractionated EBRT+HDR-IRT boost. The results showed no significant differences in terms of GU and GI toxicities among the two

Table III. *Toxicity (CTAE v4.03), IMRT+IRT had a lower risk of acute GU toxicity.*

	Tomotherapy			VMAT			VMAT+HDR-IRT		
	G1	G2	G3	G1	G2	G3	G1	G2	G3
GU Acute *p*=0.048	7	4	0	9	1	0	6	1	0
GU Late	0	0	0	1	0	0	2	0	0
GI Acute	4	2	0	6	2	0	4	0	0
GI Late	0	0	0	1	0	0	0	0	0

CTAE: Common Toxicity Criteria for Adverse Event; GU: genitourinary; GI: gastrointestinal; G: grade; IMRT: intensity-modulated-radiotherapy; HDR-IRT: high dose-rate interventional radiotherapy.

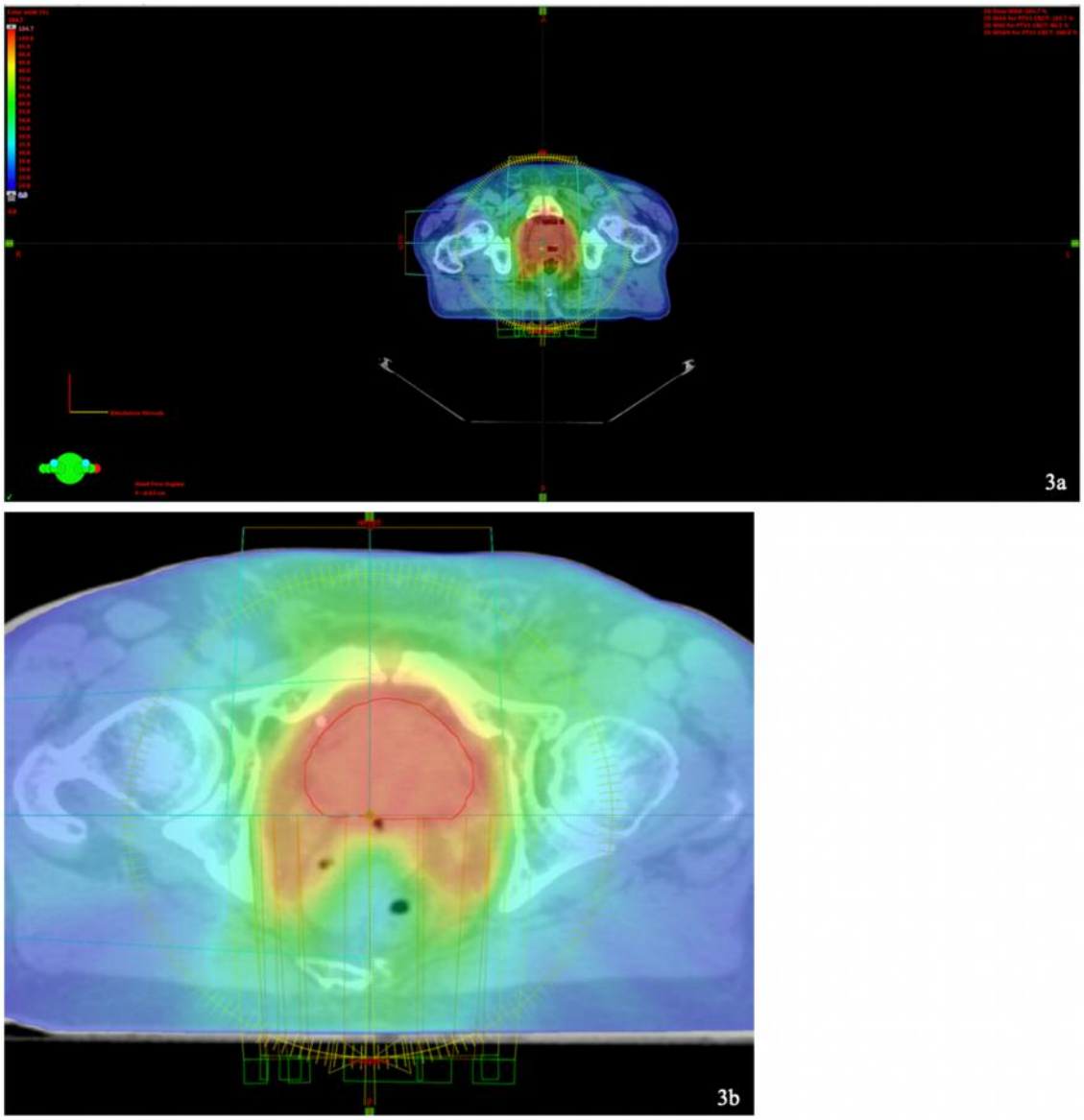

Figure 3. *Dose distribution of intensity modulated radiotherapy (IMRT). Axial views show dose distribution relative to IMRT planning target volumes (PTVs) and organs at risk (Rome 3a and Luebeck 3b).*

groups. Sathya *et al*. (21) randomized 104 patients with non-metastatic prostate cancer to either conventionally fractionated EBRT or IRT boost with conventionally fractionated EBRT. The authors reported no differences in the toxicity profile between the two arms. No studies compared different fractionation methods in the EBRT arms.

Compared to the Hoskin and Sathya studies, the present univariate analysis showed that IMRT+IRT had a lower risk of acute GU toxicity (p=0.048) while no significant differences in acute and late GI and late GU were detected. HDR-IRT boost was not related to late G2-3 GU and GI toxicities showing that the combined treatment dose-escalation could represent a valid option in intermediate-high-risk prostate cancer treatment.

In another study, Morris randomized 398 patients with intermediate- and high-risk prostate cancer to either EBRT or low dose-rate (LDR) IRT complementary to EBRT. Assessment of the 5-year cumulative incidence of late grade 3 or higher toxicities detected a significant benefit in grade 3 GU effects in favor of treatment with EBRT (p=0.001) (20). Prestidge *et al*. in 2016, randomized 588 patients with low-intermediate risk prostate cancer to EBRT with LDR boost or LDR alone. There were no differences in acute grade 3 or higher toxicity but worse grade 3 or higher late toxicity in the IRT boost arm (22).

A recent systematic review of literature evidence on HDR IRT boost in prostate cancer showed good results in terms of toxicity outcomes and survival (18). Five years rate of LR (0-8%) and OS (85-100%) were shown among low-, intermediate-, high-risk, locally advanced prostate cancer patient groups. In terms of toxicity, less than 6% Grade 3-4 late GU and GI toxicities were reported.

The differences in toxicity between these studies, but also between the IRT procedures (LDR *vs*. HDR) may be due to the ability to sparing the membranous urethra, which is associated with lower stricture rate. Using IRT it is possible to avoid patient and internal organ motion errors in treatment delivery also with the only expansion of 2 mm from clinical target volume (CTV) to planning target volume (PTV). The high-dose PTV in HDR-IRT is significantly smaller compared to that in EBRT (38-41).

Most trials used questionnaires to evaluate GU toxicity - but it might be influenced by both patient and physician bias. However, patient reported outcomes are becoming crucial in treatment choice (42).

Our results confirmed the feasibility and safety of HDR boost escalation as shown in literature in other patient settings (43-45); even if HDR has to be performed in specialized centers collecting high numbers of patients with Expert Interventional Radiation Oncologist (46, 47).

However, in the present analysis, the small sample and the retrospective nature of the study reflect the difficulty to match patients in multi-institutional cohorts. Although the dose for each treatment was similar, we compared two different EBRT techniques that could reflect different conformity of fields.

In this scenario, advances in technologies and treatments for prostate cancer but also the huge heterogeneity of tumours and patients, need to consider a lot of different variables in the decision-making process (48).

Optimal treatment for prostate cancer has to be defined according to risk assessment; nomograms and predictive models can be used in order to help treatment decision-making. Nomograms offer more accurate prediction of treatment outcomes than simple risk group analyses because of the combination of relevant prognostic variables (49).

Many studies focused on the possibility of using predictive models not only for clinical outcomes, but also for toxicity occurrence (50, 51).

The above-mentioned results should also emphasize the need to combine analysis of treatment results from different centers in large databases in order to create predictive models (52, 53).

Conclusion

This preliminary study encourages the use of HDR-IRT as a local boost in dose escalated schedules for the radical treatment of intermediate- and high-risk prostate cancer. Less acute GU toxicity was observed in patients undergoing HDR-IRT boost even if focal ultra-high-dose (50 Gy IMRT+2×15 Gy HDR-IRT boost resulting in EQD2 158 Gy) was applied.

These findings support the hypothesis that focal ultra-high dose escalation is possible with IMRT+HDR-IRT if biological planning was performed.

Moreover, tolerance in HDR-IRT boost plus IMRT appeared to be comparable to exclusive IMRT and HT, while we need a longer follow-up to confirm the excellent results even in terms of survival outcomes.

A longer observation of this retrospective cohort and prospective data collection are desirable to confirm these preliminary results.

Conflicts of Interest

The Authors have declared no conflicts of interest regarding this study.

Authors' Contributions

Conception and design: Vincenzo Valentini, György Kovács, Cynthia Aristei and Giovanna Mantini; Data Collection: Andrea D'Aviero, Antonio Piras, Christian Staackmann, Simonetta Saldi; Analysis and interpretation of data: Vincenzo Frascino, Francesco Catucci, Bruno Fionda; Manuscript Writing: Anna Rita Alitto, Luca Tagliaferri, Valentina Lancellotta.

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