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Multiparametric imaging guided HDR interventional radiotherapy (brachytherapy) boost in localized prostate cancer: a multidisciplinary experience

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Abstract. – OBJECTIVE: The aim of this study was to report a monoinstitutional multidisciplinary experience about the use of multiparametric imaging to identify the areas with higher risk of relapse in localized prostate cancer, with the purpose of allowing a biologically planned target dose escalation.

PATIENTS AND METHODS: We performed a retrospective evaluation of patients diagnosed with prostate cancer who received treatments at our Interventional Oncology Center with interstitial interventional radiotherapy from 2014 to 2022. Inclusion criteria were histologically confirmed localized prostate cancer; and National Comprehensive Cancer Network (NCCN) risk class unfavorable intermediate or high/very high risk. The diagnostic work-up included multiparametric Magnetic resonance imaging (MRI), multiparametric Transrectal ultrasound (TRUS), Positron Emission Tomography Computed Tomography (PET-CT) with choline or PSMA (or alternatively bone scan). All patients were assessed and received one treatment with interstitial high-dose-rate interventional radiotherapy (brachytherapy) delivering external beam radiotherapy (46 Gy). All procedures were performed using transrectal ultrasound guidance under general anesthesia and the prescribed doses were 10 Gy to the whole prostate, 12 Gy to the peripheral zone and 15 Gy to the areas at risk.

RESULTS: We report the data of 21 patients who were considered for the statistical analysis with a mean age of 62.5 years. The mean PSA nadir was 0.03 ng/ml (range 0-0.09). So far, no biochemical nor radiological recurrences have been recorded in our series. Regarding acute toxicity, the most commonly reported side effects were G1 urinary in 28.5% of patients and G2 urinary in 9.5%; all recorded acute toxicities resolved spontaneously.

CONCLUSIONS: We present a real-life experience of biologically planned local dose escalation by interventional radiotherapy (brachytherapy) boost, followed by external beam radiotherapy in patients with intermediate unfavorable- or high/very high risk. The local control and the biochemical control rates are proved to be excellent and the toxicity profile tolerable.

Key Words:
Prostate cancer, Radiotherapy, Interventional radiotherapy, Brachytherapy.

Introduction

Radiotherapy for localized prostate cancer has proven to be an effective alternative to radical prostatectomy[1]. In this clinical setting, the treatment decision should always be based on the stage/risk group of the disease. Potential treatment outcomes and side effects related to surgery and to radiotherapy should be discussed with the patient in a multidisciplinary setting, and the patient must be invited to express a preference[2].

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Multidisciplinary management of prostate cancer allows patients to be correctly staged and, therefore, to access the best therapeutic options, balancing advantages and side effects[3].

Multiparametric imaging including MRI, PET-CT, and TRUS have proven to be by far superior to standard imaging in terms of accuracy for the diagnosis of prostate cancer lesions[4,5], and combining these diagnostic approaches has shown to further increase sensitivity and ability to detect the cancerous lesions[6].

The use of multiparametric imaging also plays a pivotal role in guiding clinicians to target their biopsies, thus allowing them to obtain histologic confirmation before deciding the optimal treatment strategy[7].

The need for a clear identification of intraprostatic lesions relies on the clinical evidence that the typical site of recurrence, after radiotherapy, occurs within the dominant intraprostatic lesion (DIL)[8]. This point is of crucial importance because it has been demonstrated that there is a clear relationship between the dose delivered to the DIL and risk of relapse: patients receiving higher doses do have a lower risk of recurrence[9,10].

Advanced technological options, such as intensity-modulated radiotherapy (IMRT) have made it possible to reduce the risk of radiation-induced side effects, thus allowing for the pursuit of an increasing dose escalation[11].

In particular, interventional radiotherapy (IRT), known also as brachytherapy (BT), allows clinicians to deliver a higher target dose in combination with a lower dose to organs at risk (OAR), thanks to its physical properties, compared to external beam radiotherapy (ERT) as underlined by the recent The Groupe Européen de Curiethérapie (GEC), the European SocieTy for Radiotherapy & Oncology (ESTRO), and the Advisory Committee for Radiation Oncology Practice (ACROP) guidelines[12].

The aim of this study is to report a monoinstitutional multidisciplinary experience about the use of multiparametric imaging to identify the areas with higher risk of relapse in localized prostate cancer, with the purpose of pursuing a biologically planned target dose escalation using a sequential approach of interventional radiotherapy followed by external beam radiotherapy.

Patients and Methods

We performed a retrospective evaluation of patients diagnosed with prostate cancer who received treatments at our Interventional Oncology Center (IOC)[13] with interstitial IRT from 2014 to 2022.

Patients were identified through the electronic database Speed RO, which allowed us to retrospectively retrieve anonymized patients' data, thus fully respecting the General Data Protection Regulations (GDPR)[14,15].

Overall, 36 patients were identified. However, for statistical purposes, patients lost to follow-up or with follow-up of less than 12 months were excluded from the analysis (15 patients).

Inclusion criteria were histologically confirmed localized prostate cancer, available data on pretreatment PSA level, age 18 years or higher, NCCN risk class unfavorable intermediate or high/very high risk, and treatment with IRT HDR pre-boost.

In all patients, the diagnostic work-up included multiparametric MRI, multiparametric TRUS, PET-CT with choline or Prostate-specific membrane antigen (PSMA), or alternatively bone scan; additionally, all patients were evaluated with a basal uroflowmetry and were asked to complete an International Prostatic Symptoms Score (IPSS) questionnaire and an International Index of Erectile Function (IIEF 5) questionnaire.

Patients were asked to fill in the questionnaires at base line (before IRT), during the first visit after radiotherapy, after six months, and then once a year. Patients' characteristics are reported in Table I.

The implant procedure included three different phases: pre-planning, implantation, and on-line treatment planning and delivery (Table II).

In the pre-planning phase, all cases were discussed in a multidisciplinary setting, including an interventional radiation oncologist, a radiologist,

Table I. Patients' characteristics.

Factors	% (n)
Age (mean)	62.5 years (range 61–81)
T stage	
2a	9.5% (2)
2c	19% (4)
3a	33.4% (7)
3b	38.1% (8)
N stage	
N−	100% (21)
N+	0
ISUP	
1	14.3% (3)
2	19% (4)
3	38.1% (8)
4	14.3% (3)
5	14.3% (3)
Follow-up (mean)	60 months (range 14-103)

Table II. Procedure steps.

Step 1: Pre-planning
a. mpMRI and PET-CT (when available) to define the high-risk areas b. Identification of positive biopsies within the prostate c. mpTRUS evaluation of the sub-CTVs within the target d. Multidisciplinary discussion
Step 2: Implant technique
a. TRUS guided needles insertion carefully avoiding injury to the urethra b. Needles fixed to the template for better stability
Step 3: Treatment planning and delivery
a. TRUS-based reconstruction of the actual needle positions for 3D treatment planning b. Target definition based on multidisciplinary agreement c. TRUS-based real-time IRT planning and dose volume optimization d. Treatment delivery

and a nuclear medicine physician. Information from mpMRI, PET-CT, and mpTRUS was gathered with the histology data of the positive cores in order to identify three different volumes: the prostate (CTV1), the peripheral zone (CTV2), and the high-risk zone (CTV3).

In particular, the high-risk zone (CTV3) was graphically identified as shown in Figure 1.

It is important to underline that the final CTV 3 considered the sum of the different areas at risk coming from multiparametric imaging and from biopsies in all patients.

The mpTRUS evaluation allowed clinicians to identify patients with adequate prostate volume (to be included within the template), to study the distance between the prostate and the rectal mucosa (>5mm), and to prevent the possibility of public arc interference.

Regarding the implant technique, in all cases we used metal needles, inserted them into the prostate template by TRUS guidance under general anesthesia, and placed them mainly in accordance with the Paris system rules in order to provide adequate coverage of the three different volumes identified. A urinary catheter was placed in all patients before the implant procedure so as to better visualize the urethra on TRUS.

Local fixation was obtained first through anchor needles and then using the dedicated template. The total number of catheters varied according to the CTV size. The entire procedure was performed under general anesthesia.

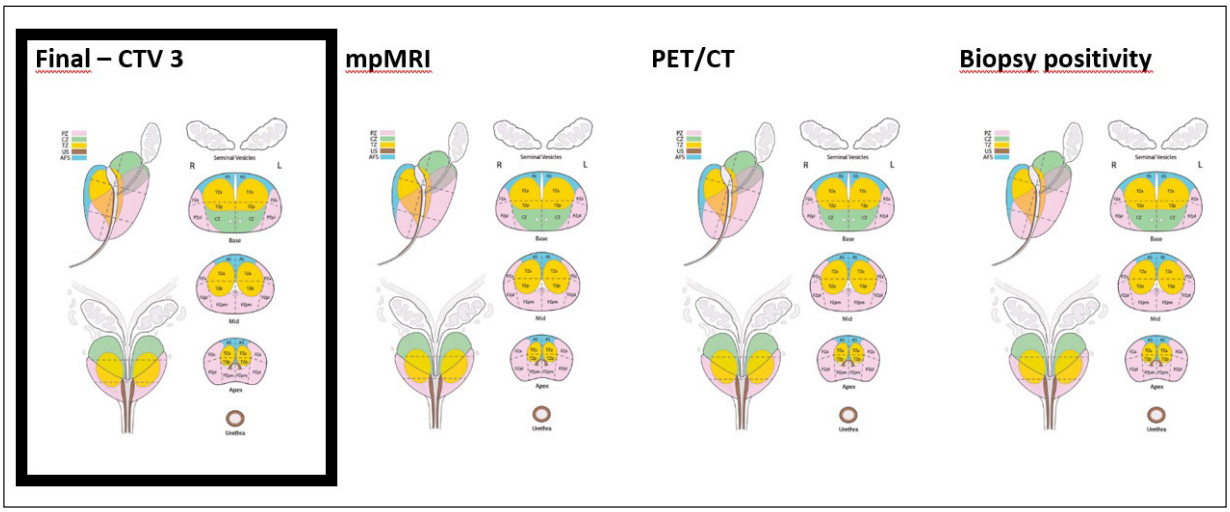

Figure 1. Multiparametric CTV identification (Modified from reference 16).

Regarding the treatment planning, mpTRUS images were used to contour the three different CTVs and TRUS volume images in order to digitally reconstruct the catheters. The treatment plan was calculated using Oncentra Brachy system v. 4.6.2 (Elekta, Stockholm, Sweden), and treatment delivery was performed using a high-dose-rate (HDR) after loader (MicroSelectron or Flexitron, Elekta, Stockholm, Sweden).

The doses prescribed to the different volumes were 10 Gy to the whole prostate, 12 Gy to the peripheral zone, and 15 Gy to the areas at risk, respectively. The OARs constraints used according to the internal protocol were rectal wall D2cc <75 Gy EQD2 (<10 Gy/fx), rectal wall V13Gy=0, urethra D0.1cc <120 Gy EQD2 (<16 Gy/fx), urethra D10 <120 Gy EQD2 (<16 Gy/fx), and urethra D30 <105 Gy EQD2 (<14 Gy/fx).

Within 10 days of completing the interventional radiotherapy, all patients started external beam radiotherapy with a total dose of 46 Gy in 2 Gy fraction to the prostate and to the regional pelvic nodes for those at risk of nodal metastases >15% based on Roach's formula[17].

Androgen deprivation therapy (ADT) was given according to NCCN guidelines with regard to risk classes and timing. Acute and late toxicities were assessed according to the Radiation Therapy Oncology Group (RTOG)[18].

Data from the collected cases were collated and processed using the Data Analysis ToolPak loaded in Excel (Microsoft®, Redmond, Washington, USA) to calculate descriptive statistics.

Results

We report the data of 21 patients who were considered for the statistical analysis.

The mean age was 62.5 years (range 61-81) and the rate of patients with T2a, T2c, T3a, and T3b tumor stage was 9.5%, 19%, 33.3%, and 38%, respectively.

The mean number of biopsies was 13 (range 8-30) and the relative percentage of positive cores was 35% (range 3-90). None of the included patients had positive lymph nodes.

The mean prostatic volume was 32cc and the mean PSA level at diagnosis was 11.8 ng/ml (range 3.3-61).

Mean rectal wall D2cc was 7.8 Gy (range 5.4-10.2), mean urethra D30 was 12.6 Gy (range 7.4-16), mean urethra D10 was 13.4 Gy (9.3-16), and mean urethra D0.1cc was 12.9 Gy (range 8.5-16).

The mean PSA nadir was 0.03 ng/ml (range 0-0.09), and almost all patients reached the nadir at the first follow-up visit 2 months after completing radiotherapy.

So far, no biochemical nor radiological recurrences have been recorded in our series.

Regarding acute toxicity, the most commonly reported side effects were G1 urinary in 28.5% of patients and G2 urinary in 9.5%; all recorded acute toxicities resolved spontaneously. No late toxicities were recorded in our patients. Moreover, no significant changes of either IPSS or IIEF 5 were noticed.

The median follow-up time was 60 months (range 14-103). Figures 2, 3 and 4 present an example of a typical implant.

Discussion

In this analysis, we present the preliminary results of an innovative treatment strategy for intermediate, unfavorable, high, and very high-risk prostate cancers, based on an anticipated image-guided boost on the DIL delivered with HDR-IRT, and followed by EBRT, on the prostate +/- pelvic lymph nodes. The DIL definition was performed using multiple functional imaging methods.

The use of three different imaging modalities, in combination with the information of the biopsy mapping, had the aim of achieving the maximum possible sensitivity in defining the full extent of the DIL. In fact, some studies have shown that single methods may have limited sensitivity in the precise definition of the target in the DIL boosts[19].

The preliminary results of our study, on a sample of 21 patients, showed excellent tolerability of the treatment and the absence of biochemical or clinical relapses. These results, albeit with the limitations of a numerically limited sample, seem to confirm other evidence from the literature on boost by IRT on DIL in radiotherapy of prostate cancer.

Regarding the patients excluded from the statistical analysis, in most cases the reason was the short follow-up time, but there were also a few cases of patients lost to follow-up because living far from hospital, as it is a large tertiary center where patients are referred by clinicians from different regions of the country.

In a few cases, as reported in Table I, patients were ISUP 1-2; however according to NCCN risk group definitions they were unfavorable intermediate due either to ≥ 50% biopsy cores positive or to the concomitant presence of cT2b-cT2c and PSA 10-20 ng/mL.

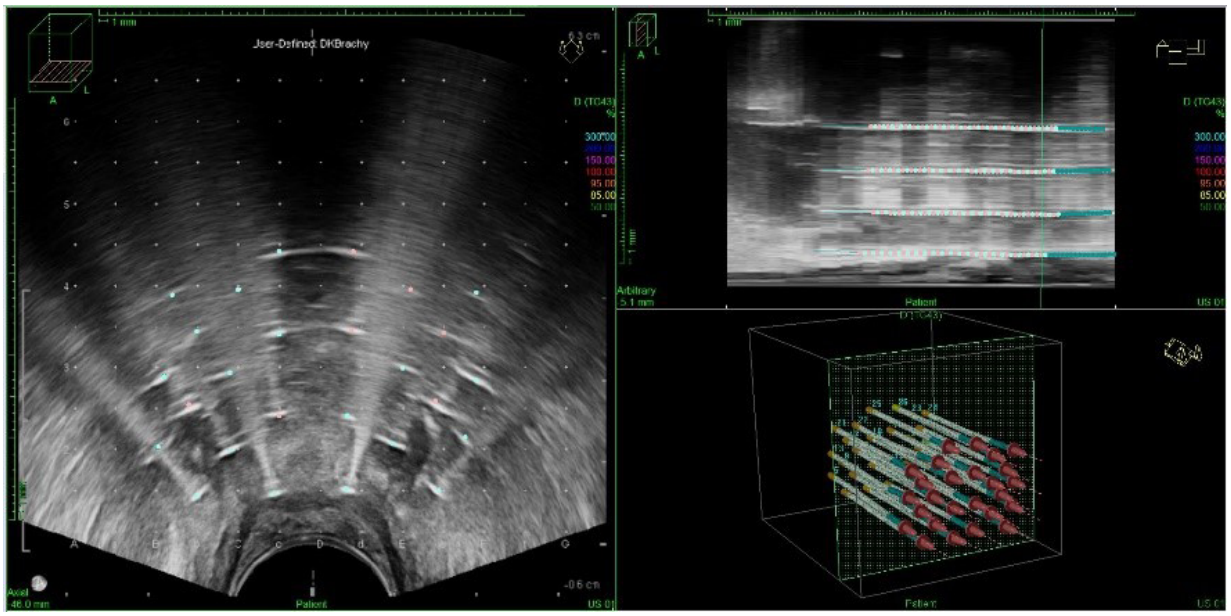

Figure 2. Needles reconstruction.

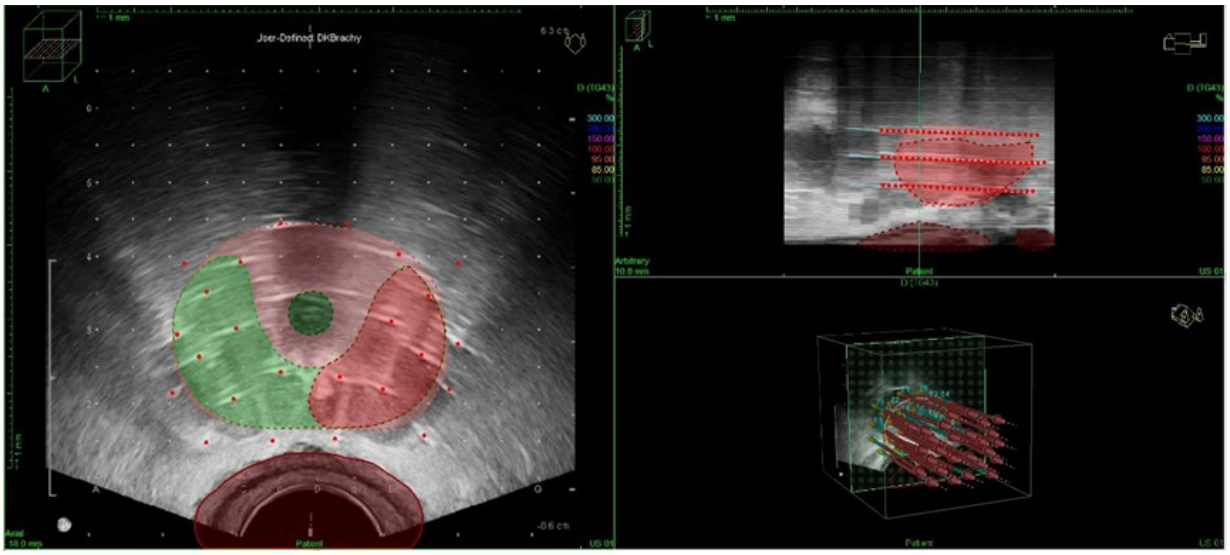

Figure 3. Prostate after implantation with contoured volumes.

In the context of interstitial IRT for prostate cancer, there are several aspects that should be carefully defined including the choice of the dose rate, the choice of imaging for the simulation phase, and the association in the case of "boost" with ERT.

Regarding the dose rate in the treatment of prostate cancer, IRT can be delivered by interstitial implantation of permanent seeds (Low-Dose Rate - LDR)[20] or by temporary interstitial application of High-Dose Rate (HDR) sources21. Clinical data available from retrospective studies[20-22] on these two different approaches show that they can both be considered effective in terms of tumor control.

Looking to the possible integrations of IRT with modern multiparametric imaging techniques, the introduction of transrectal ultrasound (TRUS) into clinical practice has opened up new, revolutionary possibilities, especially for the interstitial application of temporary HDR[23].

In fact, from a technical point of view, IRT HDR can be performed by using different

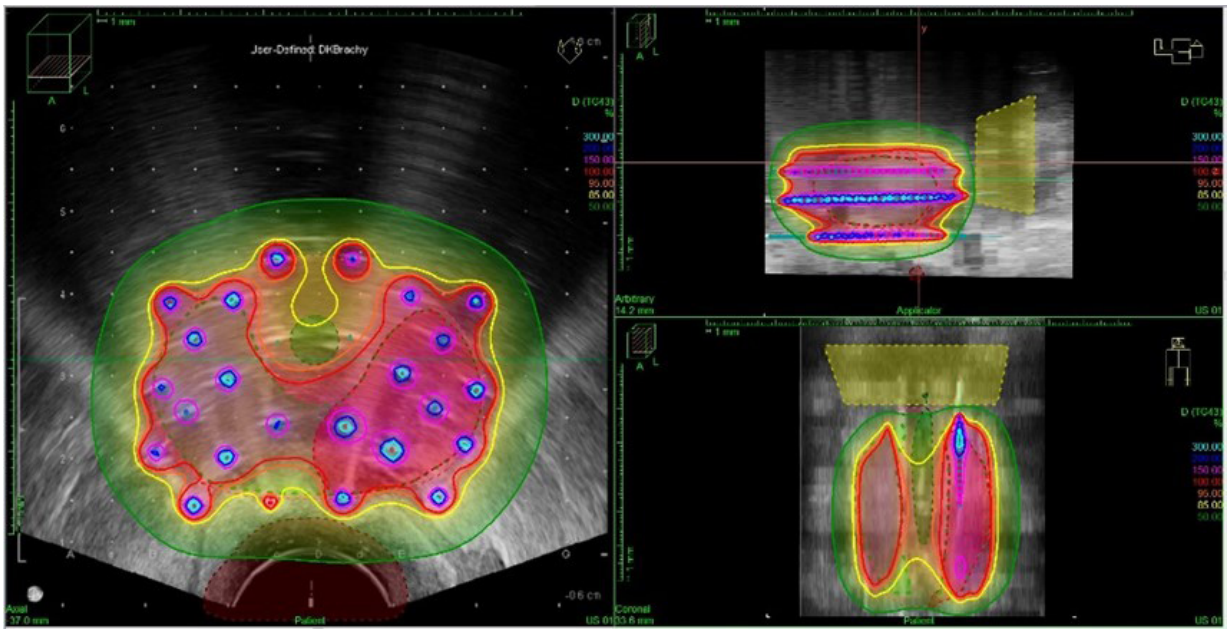

Figure 4. Dose distribution.

imaging modalities for planning such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and multiparametric transrectal ultrasound (mpTRUS). The choice of the imaging modality can vary between different centers considering the different levels of experience and availability of technological equipment: however, the choice of mpTRUS has been proved extremely useful for several reasons[24].

The possibility of relying on an mpTRUS allows clinicians to reach very high doses in the areas that are at the greatest risk of prostate recurrence, thus obtaining excellent tumor control and OARs sparing at the same time with very low late toxicity[25].

From a procedural point of view, the approach that uses ultrasound as imaging for planning has a prerogative that cannot be obtained with the use of CT or MRI since the procedure, which is usually performed under general anesthesia (for a duration of about 3 hours), does not require the patient to be moved during the entire procedure. This results in the stability of the inserted needles, which is absolutely guaranteed.

The use of mpTRUS offers several advantages, especially regarding on-line planned sub-volume dose escalation to dominant high-Gleason areas and have led to a re-evaluation of the role of HDR IRT in the prostate also in relation to LDR.

Particularly if we consider the α/β ratio around 1.5, this allows us to assume that the therapeutic choice favors the hypofractionated radiation approach[26] in principle.

In addition to this, it has recently been shown that a high fraction dose of HDR IRT induces transcriptional changes in the tumor genome, which increase its sensitivity to subsequent exposure to radiation, whether the further treatment is interventional radiotherapy or external beam radiotherapy[27].

Another advantage to underline is related to the fact that the implant is temporary in the case of HDR IRT, and no radioactivity remains in the patient at the end of the session[28].

A further potential positive aspect concerns the purely dosimetric topic. In the particular case of the LDR IRT, there is only a restricted possibility of local dose modulation. From a dosimetric point of view, it is easily feasible with HDR due to the flexible volume dose modulation potential of the stepping source technology compared with biological imaging qualities. The target (and the sub-volumes) dose can be modulated according to the needs of dose coverage to the specific CTV and to organs at risk (OAR)[29].

Also, the presence of significant intraprostatic calcifications can worsen the distribution of the radiation dose in case of LDR IRT, with a possible significant effect on disease control. On the contrary, this problem is absolutely marginal in HDR, which uses higher energies and, therefore, is not significantly affected by the presence of calcifications[30].

An element still to be considered is related to the side effect profile; if on the one hand it is true that the toxicity profile tends to be superimposable from a time point of view, it should be emphasized that in the case of HDR IRT, the symptoms tend to reach the peak earlier and resolve more quickly, typically in a few days rather than weeks or months as it is common with LDR IRT[31].

Regarding the use of HDR IRT as a boost, data with mature follow-up exceeding 10 years are now available in the literature.

In particular, a recent randomized phase-3 study[32] included 216 patients with localized prostate cancer. Of these, 106 were randomized to ERT alone, while 106 were assigned to ERT+IRT HDR. With a follow-up that exceeded 12 years, the authors demonstrated a significant impact of adding HDR IRT in terms of relapse-free survival.

Also, with regard to acute side effects, we have large series of cases in the literature that testify how the combination of IRT HDR and ERT is characterized by a favorable profile. In a study that included 338 patients receiving combined treatments, late rectal effects after five years were present in only 0.3% of treated patients[33].

Also, in geriatric patients, IRT HDR boost may be delivered safely as recently demonstrated in a large cohort[34].

In terms of the timing of the interventional radiotherapy boost in various centers, there are different clinical experiences. Some groups use the interventional approach after external beam radiotherapy, while other authors use the IRT HDR as a pre-boost[35,36].

Retrospective evidence, in which both disease control and toxicity were analyzed, showed no statistically significant differences between the two types of approaches; they are therefore both feasible[37].

Both medical and physical quality assurance programs are extremely important. Introducing dedicated checklists may help RTTs, physicists, and nurses cooperate in a coordinated manner[38,39].

The need for a specific training module with a learning curve was also repeatedly reported[40,41]. In this regard, it is important to underline the role of educational activities aimed at promoting training for interventional radiation oncologists who are willing to learn this kind of technique[42,43].

In terms of cost-effectiveness, HDR IRT was proven to be less expensive when compared to ERT[44].

There is growing evidence in the literature, including from prospective studies, that focal dose escalation using ultrasound may be regarded as safe and effective[45].

An additional element to consider in the future is artificial intelligence (AI). AI may play a key role in merging the data coming from the different imaging modalities and from histology in order to automatically obtain the high-risk areas of the prostate[46], as well as in future robot-assisted implantations[47,48].

To the best of our knowledge, this is the first experience on the combined use of mpMRI, PET-CT, mpTrUS, and biopsy mapping for the definition of the target in the setting of IRT-boost on the DIL of prostate carcinoma. Further studies are needed to: i) evaluate the long-term results of this treatment strategy on larger patient populations, ii) evaluate the pattern of failure in patients undergoing this treatment modality in order to further optimize its results, and iii) to evaluate whether AI systems, in particular radiomics analyses, can further improve the definition of the target in the boost on DIL.

Limitations

Our study has some limitations: i) the retrospective design, with the consequent risk of patient selection bias, ii) the low sample size, and iii) a still short follow-up in at least half of the patients, with consequent limitations in the evaluation of late toxicity and biochemical and clinical outcome.

Conclusions

We present a real-life experience of biologically planned local dose escalation through interventional radiotherapy (brachytherapy) boost, followed by external beam radiotherapy in patients with intermediate, unfavorable, or high/very high risk. The local control and the biochemical control rates are proved to be excellent, and the toxicity profile is shown to be tolerable, consistently with the literature. Further studies, with larger cohorts and longer follow-up periods are desirable in order to confirm our preliminary data.

Authors' Contributions

Conceptualization, L.T.; methodology, A.R.A. and V.F.; formal analysis, F.C. and V.L.; resources, G.A.; data curation, E.P.; writing-original draft preparation, B.F.; final approval, A.G.M., G.K., A.G. R.M and V.V. All authors have read and agreed to the published version of the manuscript.

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Ethics Approval
The study was conducted in accordance with the Declaration of Helsinki, and ethical review and approval were provided (Prot. No. 0012205/15); this retrospective study was conducted according to the principles of good clinical practice and in accordance with GDPR regulations for privacy.

Informed Consent
Informed consent was obtained from each participant included in the study.

Conflicts of Interest
The authors declare no conflict of interest.

Data Availability
Not applicable.

References

1) Wallis CJD, Saskin R, Choo R, Herschorn S, Kodama RT, Satkunasivam R, Shah PS, Danjoux C, Nam RK. Surgery Versus Radiotherapy for Clinically localized Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol 2016; 70: 21-30.
2) Wang Z, Ni Y, Chen J, Sun G, Zhang X, Zhao J, Zhu X, Zhang H, Zhu S, Dai J, Shen P, Zeng H. The efficacy and safety of radical prostatectomy and radiotherapy in high-risk prostate cancer: a systematic review and meta-analysis. World J Surg Oncol 2020; 18: 42.
3) Sciarra A, Gentile V, Panebianco V. Multidisciplinary management of Prostate Cancer: how and why. Am J Clin Exp Urol 2013; 1: 12-17.
4) Granata V, Bicchierai G, Fusco R, Cozzi D, Grazzini G, Danti G, De Muzio F, Maggialetti N, Smorchkova O, D'Elia M, Brunese MC, Grassi R, Giacobbe G, Bruno F, Palumbo P, Grassi F, Brunese L, Grassi R, Miele V, Barile A. Diagnostic protocols in oncology: workup and treatment planning. Part 2: Abbreviated MR protocol. Eur Rev Med Pharmacol Sci 2021; 25: 6499-6528.
5) Mannaerts CK, Wildeboer RR, Remmers S, van Kollenburg RAA, Kajtazovic A, Hagemann J, Postema AW, van Sloun RJG, J Roobol M, Tilki D, Mischi M, Wijkstra H, Salomon G. Multiparametric Ultrasound for Prostate Cancer Detection and Localization: Correlation of B-mode, Shear Wave Elastography and Contrast Enhanced Ultrasound with Radical Prostatectomy Specimens. J Urol 2019; 202: 1166-1173.
6) Chen M, Zhang Q, Zhang C, Zhao X, Marra G, Gao J, Lv X, Zhang B, Fu Y, Wang F, Qiu X, Guo H. Combination of 68Ga-PSMA PET/CT and Multiparametric MRI Improves the Detection of Clinically Significant Prostate Cancer: A Lesion-by-Lesion Analysis. J Nucl Med 2019; 60: 944-949.
7) Gayet M, van der Aa A, Beerlage HP, Schrier BP, Mulders PF, Wijkstra H. The value of magnetic resonance imaging and ultrasonography (MRI/US)-fusion biopsy platforms in prostate cancer detection: a systematic review. BJU Int 2016; 117: 392-400.
8) Cellini N, Morganti AG, Mattiucci GC, Valentini V, Leone M, Luzi S, Manfredi R, Dinapoli N, Digesu' C, Smaniotto D. Analysis of intraprostatic failures in patients treated with hormonal therapy and radiotherapy: implications for conformal therapy planning. Int J Radiat Oncol Biol Phys 2002; 53: 595-599.
9) Zelefsky MJ, Pei X, Chou JF, Schechter M, Kollmeier M, Cox B, Yamada Y, Fidaleo A, Sperling D, Happersett L, Zhang Z. Dose escalation for prostate cancer radiotherapy: predictors of long-term biochemical tumor control and distant metastases-free survival outcomes. Eur Urol 2011; 60: 1133-1139.
10) Daly T, Hickey BE, See AM, Francis DP. Dose-escalated radiotherapy for clinically localised and locally advanced prostate cancer. Cochrane Database Syst Rev 2017; 11: CD012817.
11) Zietman AL, DeSilvio ML, Slater JD, Rossi CJ Jr, Miller DW, Adams JA, Shipley WU. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. JAMA 2005; 294: 1233-1239.
12) Henry A, Pieters BR, André Siebert F, Hoskin P; UROGEC group of GEC ESTRO with endorsement by the European Association of Urology. GEC-ESTRO ACROP prostate brachytherapy guidelines. Radiother Oncol 2022; 167: 244-251.
13) Kovács G, Tagliaferri L, Valentini V. Is an Interventional Oncology Center an advantage in the service of cancer patients or in the education? The Gemelli Hospital and INTERACTS experience. J Contemp Brachytherapy 2017; 9: 497-498.
14) Valentini V, Maurizi F, Tagliaferri L, Balducci M, Cellini F, Gambacorta MA, Lanzotti V, Manfrida S, Mantini G, Mattiucci GC, Meduri B, Micciche F, Nardone L, D'agostino GR. Spider: Managing clinical data of cancer patients treated through a multidisciplinary approach by a palm based system. Ital J Public Health 2008; 5: 154-164.
15) Lancellotta V, Guinot JL, Fionda B, Rembielak A, Di Stefani A, Gentileschi S, Federico F, Rossi E, Guix B, Chyrek AJ, Meritxell A, Villalba SR, Colloca GF, Dinapoli N, Masciocchi C, Lenkowicz J, Capocchiano ND, Damiani A, Valentini V, Kovács G, Tagliaferri L. SKIN-COBRA (Consortium for Brachytherapy data Analysis) ontology: The first step towards interdisciplinary standardized data collection for personalized oncology in skin cancer. J Contemp Brachytherapy 2020; 12: 105-110.
16) Purysko AS, Rosenkrantz AB, Turkbey IB, Macura KJ. RadioGraphics Update: PI-RADS Version 2.1-A Pictorial Update. Radiographic 2020; 40: E33-E37.

17) Roach M 3rd, Marquez C, Yuo HS, Narayan P, Coleman L, Nseyo UO, Navvab Z, Carroll PR. Predicting the risk of lymph node involvement using the pre-treatment prostate specific antigen and Gleason score in men with clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 1994; 28: 33-37.

18) Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995; 31: 1341-1346.

19) Alfano R, Bauman GS, Liu W, Thiessen JD, Rachinsky I, Pavlosky W, Butler J, Gaed M, Moussa M, Gomez JA, Chin JL, Pautler S, Ward AD. Histologic validation of auto-contoured dominant intraprostatic lesions on [18F] DCFPyL PSMA-PET imaging. Radiother Oncol 2020; 152: 34-41.

20) Grimm P, Billiet I, Bostwick D, Dicker AP, Frank S, Immerzeel J, Keyes M, Kupelian P, Lee WR, Machtens S, Mayadev J, Moran BJ, Merrick G, Millar J, Roach M, Stock R, Shinohara K, Scholz M, Weber E, Zietman A, Zelefsky M, Wong J, Wentworth S, Vera R, Langley S. Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. BJU Int 2012; 109: 22-29.

21) Challapalli A, Jones E, Harvey C, Hellawell GO, Mangar SA. High dose rate prostate brachytherapy: an overview of the rationale, experience and emerging applications in the treatment of prostate cancer. Br J Radiol 2012; 85: S18-S27.

22) Skowronek J. Low-dose-rate or high-dose-rate brachytherapy in treatment of prostate cancer - between options. J Contemp Brachytherapy 2013; 5: 33-41.

23) Hoskin PJ, Colombo A, Henry A, Niehoff P, Paulsen Hellebust T, Siebert FA, Kovacs G. GEC/ESTRO recommendations on high dose rate afterloading brachytherapy for localized prostate cancer: an update. Radiother Oncol 2013; 107: 325-332.

24) Hoskin P. High dose rate brachytherapy for prostate cancer. Cancer Radiother 2008; 12: 512-514.

25) Kovács G, Müller K, Soror T, Melchert C, Guo X, Jocham D, Merseburger A. Results of multiparametric transrectal ultrasound-based focal high-dose-rate dose escalation combined with supplementary external beam irradiation in intermediate- and high-risk localized prostate cancer patients. Brachytherapy 2017; 16: 277-281.

26) Brenner DJ, Martinez AA, Edmundson GK, Mitchell C, Thames HD, Armour EP. Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio), similar to late-responding normal tissue. Int J Radiat Oncol Biol Phys 2002; 52: 6-13.

27) Keam SP, Caramia F, Gamell C, Paul PJ, Arnau GM, Neeson PJ, Williams SG, Haupt Y. The Transcriptional Landscape of Radiation-Treated Human Prostate Cancer: Analysis of a Prospective Tissue Cohort. Int J Radiat Oncol Biol Phys 2018; 100: 188-198.

28) Slessinger ED. Practical considerations for prostate HDR brachytherapy. Brachytherapy 2010; 9: 282-287.

29) Cosset JM, Haie-Meder C. Brachytherapy for prostate cancer: high dose rate or low-dose rate? Cancer Radiother 2005; 9: 610-619.

30) Vigneault E, Mbodji K, Carignan D, Martin AG, Miksys N, Thomson RM, Aubin S, Varfalvy N, Beaulieu L. The association of intraprostatic calcifications and dosimetry parameters with biochemical control after permanent prostate implant. Brachytherapy 2019; 18: 787-792.

31) Crook J, Marbán M, Batchelar D. HDR Prostate Brachytherapy. Semin Radiat Oncol 2020; 30: 49-60.

32) Hoskin PJ, Rojas AM, Ostler PJ, Bryant L, Lowe GJ. Randomised trial of external-beam radiotherapy alone or with high-dose-rate brachytherapy for prostate cancer: Mature 12-year results. Radiother Oncol 2021; 154: 214-219.

33) Tamihardja J, Lutyj P, Kraft J, Lisowski D, Weick S, Flentje M, Polat B. Two-Weekly High-Dose-Rate Brachytherapy Boost After External Beam Radiotherapy for Localized Prostate Cancer: Long-Term Outcome and Toxicity Analysis. Front Oncol 2021; 11: 764536.

34) Marotte D, Gal J, Schiappa R, Gautier M, Boulahssass R, Chand-Fouche ME, Hannoun-Levi JM. High-dose-rate brachytherapy boost for elderly patients with intermediate to high-risk prostate cancer: 5-year clinical outcome of the PROSTAGE cohort. Clin Transl Radiat Oncol 2022; 35: 104-109.

35) Alitto AR, Tagliaferri L, Lancellotta V, D'Aviero A, Piras A, Frascino V, Catucci F, Fionda B, Staackmann C, Saldi S, Valentini V, Kovacs G, Aristei C, Mantini G. BIT-ART: Multicentric Comparison of HDR-brachytherapy, Intensity-modulated Radiotherapy and Tomotherapy for Advanced Radiotherapy in Prostate Cancer. In Vivo 2020; 34: 1297-1305.

36) Kazi A, Godwin G, Simpson J, Sasso G. MRS-guided HDR brachytherapy boost to the dominant intraprostatic lesion in high risk localised prostate cancer. BMC Cancer 2010; 10: 472.

37) Roy A, Brenneman RJ, Hogan J, Barnes JM, Huang Y, Morris R, Goddu S, Altman M, Garcia-Ramirez J, Li H, Zoberi JE, Bullock A, Kim E, Smith Z, Figenshau R, Andriole GL, Baumann BC, Michalski JM, Gay HA. Does the sequence of high-dose rate brachytherapy boost and IMRT for prostate cancer impact early toxicity outcomes? Results from a single institution analysis. Clin Transl Radiat Oncol 2021; 29: 47-53.

38) Smith BR, Strand SA, Dunkerley D, Flynn RT, Besemer AE, Kos JD, Caster JM, Wagner BS, Kim Y. Implementation of a real-time, ultrasound-guided prostate HDR brachytherapy program. J Appl Clin Med Phys 2021; 22: 189-214.

39) Siebert FA, Hirt M, Niehoff P, Kovács G. Imaging of implant needles for real-time HDR-brachytherapy prostate treatment using biplane ultrasound transducers. Med Phys 2009; 36: 3406-3412.

40) Brunnhoelzl D, Hanania A, Sun S, Jaramillo S, Lu L, Jhaveri P. Implementation of High-Dose-Rate, CT-Based Prostate Brachytherapy in an Academic Teaching Hospital and Residency Training Program. Cureus 2022; 14: e22494.

41) Buus S, Rylander S, Hokland S, Søndergaard CS, Pedersen EM, Tanderup K, Bentzen L. Learning curve of MRI-based planning for high-dose-rate brachytherapy for prostate cancer. Brachytherapy 2016; 15: 426-434.

42) Tagliaferri L, Vavassori A, Lancellotta V, De Sanctis V, Barbera F, Fusco V, Vidali C, Fionda B, Colloca G, Gambacorta MA, Aristei C, Corvò R, Magrini SM. Can brachytherapy be properly considered in the clinical practice? Trilogy project: The vision of the AIRO (Italian Association of Radiotherapy and Clinical Oncology) Interventional Radiotherapy study group. J Contemp Brachytherapy 2020; 12: 84-89.

43) Tagliaferri L, Kovács G, Aristei C, De Sanctis V, Barbera F, Morganti AG, Casà C, Pieters BR, Russi E, Livi L, Corvò R, Giovagnoni A, Ricardi U, Valentini V, Magrini SM; Directors of the Italian Radiation Oncology Schools. Current state of interventional radiotherapy (brachytherapy) education in Italy: results of the INTERACTS survey. J Contemp Brachytherapy 2019; 11: 48-53.

44) Chao MW, Grimm P, Yaxley J, Jagavkar R, Ng M, Lawrentschuk N. Brachytherapy: state-of-the-art radiotherapy in prostate cancer. BJU Int 2015; 116: 80-88.

45) Strnad V, Lotter M, Kreppner S, Fietkau R. Brachytherapy focal dose escalation using ultrasound-based tissue characterization by patients with non-metastatic prostate cancer: Five-year results from single-center phase 2 trial. Brachytherapy 2022; 21: 415-423.

46) Fionda B, Boldrini L, D'Aviero A, Lancellotta V, Gambacorta MA, Kovács G, Patarnello S, Valentini V, Tagliaferri L. Artificial intelligence (AI) and interventional radiotherapy (brachytherapy): state of art and future perspectives. J Contemp Brachytherapy 2020; 12: 497-500.

47) Bi J, Zhang Y. US/MRI guided robotic system for the interventional treatment of prostate. Intern J Pattern Recognit Artif Intell 2020; 34: 5.

48) Dai X, Zhang Y, Jiang J, Li B. Image-guided robots for low dose rate prostate brachytherapy: Perspectives on safety in design and use. Int J Med Robot 2021; 17: e2239.