Simultaneous Integrated Radiotherapy Boost to the Dominant Intraprostatic Lesion: Final Results of a Phase I/II Trial

MILLY BUWENGE[1*], ANNA RITA ALITTO[2*], SAVINO CILLA[3], ILARIA CAPOCACCIA[1], ERCOLE MAZZEO[4], EDY IPPOLITO[5], GIOVANNA MANTINI[6], GIAMBATTISTA SIEPE[1], LETIZIA CAVALLINI[1], VINCENZO VALENTINI[6], FRANCESCO DEODATO[7], ALESSIO G. MORGANTI[1] and GABRIELLA MACCHIA[7]

[1]Radiation Oncology Center, Department of Experimental, Diagnostic and Specialty Medicine - DIMES,
University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy;
[2]UOC di Radioterapia Oncologica, Dipartimento Diagnostica per Immagini, Radioterapia
Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy;
[3]Medical Physic Unit, Gemelli Molise Hospital, Campobasso, Italy;
[4]Radiotherapy Unit - Department of Oncology and Hematology, University Hospital of Modena, Modena, Italy;
[5]Radiation Oncology, Campus Bio-Medico University of Rome, Rome, Italy;
[6]Istituto di Radiologia, Università Cattolica del Sacro Cuore, Rome, Italy;
[7]Radiotherapy Unit, Gemelli Molise Hospital, Campobasso, Italy

Abstract. *Background/Aim: Late toxicity and long-term outcomes of a phase I-II trial on patients with prostate cancer treated with an integrated boost to the dominant intraprostatic lesion (DIL) are reported. Patients and Methods: Patients were treated using intensity-modulated radiotherapy, with a simultaneous integrated boost to the DIL, defined on staging magnetic resonance imaging, delivering 72 Gy in 1.8 Gy/fraction to prostate/seminal vesicles and 80 Gy in 2 Gy/fraction to the DIL. The primary endpoint was acute toxicity and secondary endpoints were late toxicity and biochemical disease-free survival. Results: Forty-four patients were enrolled. The median follow-up was 120 (range=25-150) months. Five-year rates of grade 3 late gastrointestinal and genitourinary toxicity were 2.3% and 4.5%, respectively; only one grade 4 late genitourinary toxicity was recorded. Five-year biochemical relapse-free and overall survival rates were 95.3% and 95.5%, respectively. Conclusion: The treatment was well tolerated and achieved excellent results in terms of outcome in*

patients with low-intermediate Gleason's score and low risk of nodal metastasis.

*These Authors contributed equally to this work.

Correspondence to: Anna Rita Alitto, UOC di Radioterapia Oncologica, Dipartimento Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy. E-mail: annarita.alitto@policlinicogemelli.it

Although prostate cancer (PCa) is the second leading cause of cancer death in men, a 52% reduction in the death rate was recorded due to earlier diagnosis and evolution of treatment strategies (1). Moreover, acquiring new biological/ genetic information on an individual tumor and patient (genomics, radiomics, and other omics analysis) will probably allow an optimized and personalized clinical decision-making process in PCa (2).

Radiation therapy (RT) is a therapeutic option in different settings (exclusive, adjuvant, and salvage) and risk subgroups (3) with outcomes comparable to those of radical prostatectomy (4). Moreover, several technical advances in RT planning and delivery allow better conformation and increase of the dose to the prostate, resulting in improved therapeutic outcomes (5). In fact, some dose-escalation studies showed improved biochemical relapse-free survival (bRFS), local control (LC), metastasis-free survival (MFS) and overall survival (OS) (6, 7), although increased toxicity rates were sometimes reported (8).

Some studies showed that around 90% of local recurrences after RT were identified at the initial site of disease and particularly at the dominant intra-prostatic lesion (DIL) (9, 10). The identification of the DIL requires advanced imaging techniques such as multiparametric magnetic resonance imaging (MRI), positron-emission tomography with ^{11}C-choline or ^{68}Ga-prostate-specific membrane antigen, or other new-generation imaging modalities (10, 11).

Several planning studies and a few clinical trials showed that by using a simultaneous boost (SIB) to the DIL it was

Table I. *Study inclusion and exclusion criteria.*

Inclusion criteria	Biopsy-proven prostate carcinoma with a DIL detected on MRI
	DIL involving <75% of the prostate gland
	Agreement on the site of DIL between MRI and sextant biopsies
	Clinical stage T2-T3*
	Nodal risk involvement <20% (Roach formula)
	Age >18 years
	ECOG performance status ≤2
	Adequate functionality of bone marrow (Hb concentration ≥8 g/dl; WBC count ≥3,000/mm^3; PLT count ≥75,000/mm^3)
Exclusion criteria	Previous radiotherapy to the pelvis
	Nodal pelvic involvement
	Evidences of distant metastasis
	Contraindication to MRI
	Chronic inflammatory bowel disease
	Genetically proven syndrome of hyper-radiosensitivity
	History of secondary malignancy or previous invasive cancer

DIL: Dominant intraprostatic lesion; MRI: magnetic resonance imaging; ECOG: Eastern Cooperative Oncology Group; Hb: hemoglobin; WBC: white blood cell; PLT: platelet. *American Joint Committee on Cancer TNM 2002 edition (14).

feasible to increase the dose to this site while delivering standard doses to the whole prostate, thereby reducing the risks of toxicity (3, 6). However, clear evidence on this strategy are lacking due to the different patient populations enrolled, different selection criteria and techniques, and lack of randomized controlled trials.

Previously, our group published the preliminary results of a trial based on the delivery of 72 Gy to the whole prostate and 80 Gy to the DIL. This regimen resulted in outcomes comparable in terms of acute and 2-year late toxicity rates to the homogeneous irradiation of the whole prostate with lower doses (11). The aim of this analysis is to report the long-terms results on toxicities and clinical outcomes of this trial.

Patients and Methods

Study design. This was a phase I/II non-randomized trial evaluating toxicity and outcomes in a group of patients treated using IMRT with a SIB to the DIL. The study was specifically designed to evaluate the possibility to reduce the rate of acute gastrointestinal (GI) toxicity of grade 3 or more.

The incidence of this toxicity was about 50% in two randomized trials based on the delivery of high doses (>78 Gy) to the whole prostate (12, 13). Forty patients were therefore needed to achieve 80% power of reducing the rate to ≤20%. Assuming an attrition rate of 10%, particularly for the evaluation of long-term outcomes, over-recruitment was planned to compensate for drop-out after enrollment. The significance level was set at 5%. The aim of this analysis was to evaluate long-terms results for late toxicity, bRFS, LC, MFS and OS of the previous preliminary analysis (12).

Patient population. Patients were consecutively enrolled in this trial based on inclusion and exclusion criteria as detailed in Table I. Each patient underwent a preliminary evaluation including history, digital rectal examination, complete blood cell count, biochemistry panel, prostate-specific antigen (PSA), abdominal and pelvic MRI, and

bone scan. Staging was based on the American Joint Committee on Cancer TNM system 2002 edition (14). Risk of nodal involvement was calculated by the Roach's formula (15) and patients with more than 20% risk were excluded. Risk classes were defined based on the D'Amico's classification (16) as reported by National Comprehensive Cancer Network guidelines (17).

Pelvic MRI. All patients underwent T2-weighted fast spin-echo morphological sequence (axial, coronal and sagittal) MRI using 1.5-T device on a GE Sigma Scanner (GE Medical Systems, Milwaukee, WI, USA) using an endorectal coil (Medrad, Pittsburgh, PA, USA) with 4 mm slice distance. All MRIs were evaluated by an expert urologic radiologist and final stage definition and treatment decision were made during a Multidisciplinary Tumor Board. MRI was also used to identify the DIL and to verify that the DIL volume was <75% of the whole prostate.

Androgen-deprivation therapy (ADT). All patients received ADT starting 3 months before RT. ADT was prolonged to 2 years after RT in high-risk patients (defined as those with PSA >20.0 ng/ml or Gleason score >7 or stage >T2b) (16).

Radiation therapy. Details of the RT treatment planning and delivery were described in our previous report (11). All patients underwent planning with a computed tomography (CT) simulation in the supine position with a vacuum-lock bag and a knee support. To ensure homogeneous bladder filling and rectum emptying, patients had to empty the bladder and then to drink 300 ml of water 1 hour before CT simulation and before each daily fraction. Moreover, 1 hour before RT they had to void the rectum, spontaneously or using an enema. All volumes of interest were manually contoured on the CT-simulation images, while Oncentra software for image fusion (Nucletron, Columbia, MD, USA) was used to merge CT and MRI images in order to delineate the DIL on the CT scans. Cinical target volume 1 (CTV1) was the DIL plus a margin of 5 mm within the prostate. CTV2 was defined as the prostate and the seminal vesicles. A 1-cm margin was added to the CTVs (8 mm margin posteriorly) to define planning target volumes 1 (PTV1) and PTV2, respectively.

Patients were treated with five coplanar step and shoot intensity-modulated (IM) RT using 6-MV photon beams. RT doses were 72 Gy in 1.8 Gy/fraction to the prostate and seminal vesicles and 80 Gy in 2.0 Gy/fraction to the DIL using the SIB technique. Dose prescription and specification were in accordance to the ICRU 83 report (18). Before RT treatment start, all planning procedures were double-checked by sequential independent checks (19). Set-up verification was carried-out daily as previously described (20).

Patient assessment and follow-up. Patients were evaluated weekly during RT. Follow-up visits were carried out at 1 month after the end of RT, every 3 months for 2 years, every 6 months in the third to the fifth year, and annually thereafter. They included clinical examinations and PSA results. Additional studies such as bone scans or CT/MRI were planned in the case of biochemical relapse or clinical suspicion of recurrence. Toxicity was graded according to the Radiation Therapy Oncology Group scale for acute toxicity and with the Radiation Therapy Oncology Group /European Organization for Research and Treatment of Cancer for late events (21). Late toxicity was defined as an adverse event occurring after at least 3 months from the end of RT.

Statistical analysis. A descriptive analysis of the sample was carried out using the mean and standard deviation (SD) for continuous variables, and absolute and relative frequencies for categorical ones. Late toxicity, bRFS, LC, MFS, DFS, and OS were calculated from the start of RT. Survival curves were calculated using the Kaplan–Meier product-limit method (22) and compared by the log-rank test (23). Statistical analysis was carried out using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). A two-sided *p*-value of 0.05 was considered to be statistically significant.

Results

Forty-four patients with PCa (low risk: 13.6%, intermediate risk: 40.9% and high risk: 45.5%; median age=73 years, range=59-81 years) were enrolled in this prospective phase I/II trial and treated using IMRT with a SIB to the DIL. Baseline characteristics of patients and ADT are reported in Table II.

The median follow-up was 120 months (range=25-150 months); grade 3 or more acute GI and GU toxicity were recorded in two (4.5%) and one (2.3%) case, respectively. Details on acute toxicity were reported in our previous article (11). Rates of freedom from grade 1, 2, and 3 late GI toxicities at 5-years were 72.4%, 86.2%, 97.7%, and 100%, respectively. Corresponding rates for freedom from late GU toxicities were 60.8%, 90.9%, 95.5%, and 97.7%, respectively; the patient with grade 4 late GU toxicity had a history of recurrent cystitis before RT. Five-year bRFS, LC, MFS, and OS were 95.3%, 97.7%, 100.0%, and 95.5%, respectively. The corresponding 10-year rates were 90.1%, 94.9%, 97.6% and 87.8%, respectively

Discussion

In this phase I-II trial on IMRT-SIB to the DIL, we recorded acceptable toxicity and excellent treatment outcomes. These results can be partially explained by the selection criteria,

Table II. *Patient and treatment characteristics.*

Variable	Value
Age	
Median (range), years	73 (59-81)
Prostate-specific antigen	
Median (range), ng/ml	6.11 (2.28-36.00)
Distribution, n (%)	
0-10 ng/ml	37 (84.1%)
10-20 ng/ml	6 (13.6%)
>20 ng/ml	1 (2.3%)
Gleason's score, n (%)	
6	36 (81.8%)
7	8 (18.2%)
Clinical tumor stage, n (%)	
2a	6 (13.6%)
2b	9 (20.5%)
2c	10 (22.7%)
3a	11 (22.7%)
3b	8 (20.5%)
Adjuvant hormone therapy (type), n (%)	
LH-RH analog	24 (54.5%)
Bicalutamide	20 (45.5%)
Adjuvant hormone therapy	
Short-term (6 months)	24 (54.5%)
Long-term (24 months)	20 (45.5%)
Risk group*	
Low	6 (13.6%)
Intermediate	18 (40.9%)
High	20 (45.5%)

ADT: Androgen-deprivation therapy; *Defined according to the National Comprehensive Cancer Network risk classes (17).

leading to the inclusion of patients with relatively favorable prognostic features. In fact, 81.8% of the patients had Gleason's score of 6 and 97.7% of them had a PSA level <20 ng/ml.

This study had several limitations. First of all, ADT was also prescribed to patients with low-risk tumors. However, it should be noted that the trial was designed around 15 years ago, when experiences on the delivery of relatively low RT doses to the whole prostate were relatively scarce. Therefore, prudently, we chose to prescribe adjuvant ADT to all patients. This generalized use of adjuvant ADT might have had negative effects on patients' quality of life. However, it should be considered that in patients with low- to intermediate-risk disease, the duration of ADT was only 6 months, and therefore was probably associated with a slight but temporary worsening of their condition. Furthermore, RT was delivered using a relatively simple technique (step and shoot IMRT) and without fiducial markers or advanced techniques of image-guided RT. However, these issues suggest the feasibility and efficacy of this treatment modality even in less-resourced centers provided that relatively large CTV to PTV margins are used for both the prostate and the DIL, and that almost daily portal imaging is used. Moreover,

the small sample size is another limitation, even if justified by the primary endpoint and by the consequent study design. However, also in the review by Feutren and Herrera of 22 articles on prostatic RT with partial boost, only three studies included more than 100 patients and only seven reports included more than 50 patients (10). Finally, due to the small sample size and to the very small number of events, we were not able to perform any comparison between patient groups.

Comparing our results with those of the literature, we observe that our 5-year rate of bRFS (95.5%) seems higher compared to those recorded in other studies using similar techniques (85%) (10). Interestingly, this difference was recorded despite the lower equivalent dose in 2 Gy to the DIL used in our study (80 Gy) compared to the aforementioned reports (mean=89 Gy, range=80-130 Gy). Again, this difference may be explained by the favorable prognostic profile of most patients in our series.

Moreover, our results in terms of grade 3 GI and GU late 5-year toxicity (2.3% and 4.5%, respectively) are at least comparable with the series included in the Feutren and Herrera review (2.5% and 3.1%, respectively) (10). Interestingly, these similar outcomes were recorded despite the large CTV-PTV margins used in our series. The relatively low dose delivered to the DIL in our series might explain these similar results.

In terms of the generalizability of our findings, it should be stressed that our regimen might be considered particularly in patients with low-risk factors, especially in terms of Gleason score, and that we cannot be sure that the same outcome would be achieved without general use of adjuvant ADT.

In conclusion, the results of this trial suggest that the tested treatment is tolerable and able to produce good clinical results even without advanced image-guided RT systems. Therefore, our treatment technique might be suggested to less-resourced centers equipped with simple step-and-shoot IMRT and electronic portable imaging device. Obviously, when available, the use of more advanced image-guided RT techniques is recommended with the aim of reducing the CTV to PTV margins.

Finally, the results of our study and others [reviewed in (10)] justify further studies aimed at defining the optimal dose and fractionation to the prostate and to the DIL for the different prostate cancer risk categories.

Conflicts of Interest

No actual or potential conflicts of interest exist regarding this article.

Authors' Contributions

Conception and design: MB, ARA, GiM, FD, VV, FD, AGM and GaM. Data collection: MB, ARA, IC, EM, EI, GS, GiM, FD, VV and GaM. Analysis and interpretation of data: MB, ARA, SC, LC, and AGM. Article writing: MB, ARA and AGM. All Authors read and approved the final article and gave consent for its publication.

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