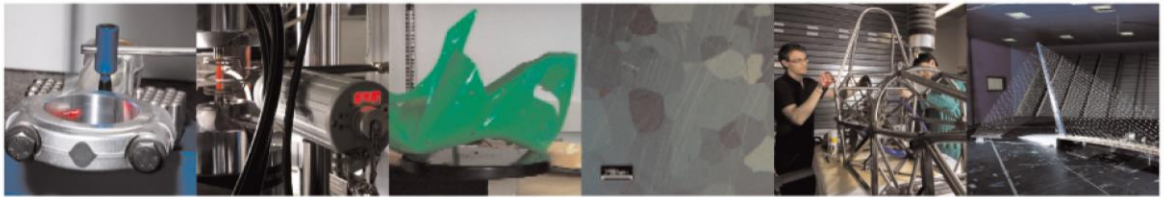




**POLITECNICO**  
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DIPARTIMENTO DI MECCANICA



## **Phase II prospective trial “Give Me Five” short-term high precision radiotherapy for early prostate cancer with simultaneous boost to the dominant intraprostatic lesion: the impact of toxicity on quality of life (AIRC IG-13218)**

Marvaso G.; Gugliandolo S.G.; Bellerba F.; Gandini S.; Corrao G.; Volpe S.; Rojas D.P.; Riva G.; Zerini D.; Pepa M.; Fodor C.I.; La Rocca E.; Pricolo P.; Alessi S.; Petralia G.; Mistretta F.A.; Cambria R.; Cattani F.; De Cobelli O.; Orecchia R.; Jereczek-Fossa B.A.

This is a post-peer-review, pre-copyedit version of an article published in MEDICAL ONCOLOGY. The final authenticated version is available online at:  
<http://dx.doi.org/10.1007/s12032-020-01397-3>

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1 **Phase II prospective trial “Give Me Five” short-term high precision radiotherapy for early**  
2 **prostate cancer with simultaneous boost to the dominant intraprostatic lesion: the impact of**  
3 **toxicity on quality of life (AIRC IG-13218)**  
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9 **Extreme hypofractionation: impact on QoL**

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12  
13 **Authors:**

14  
15 Giulia Marvaso<sup>1\*§</sup>, MD, Simone Giovanni Gugliandolo<sup>1\*</sup>, MEng, Federica Bellerba<sup>2</sup>, MSC, Sara Gandini<sup>2</sup>,  
16 PHD, Giulia Corrao<sup>1,3</sup>, MD, Stefania Volpe<sup>1,3</sup>, MD, Damaris Patricia Rojas<sup>1</sup>, MD, Giulia Riva<sup>1,3</sup>, MD, Dario  
17 Zerini<sup>1</sup>, MD, Matteo Pepa<sup>1</sup>, MEng, Cristiana Iuliana Fodor<sup>1</sup>, MSC, Eliana La Rocca<sup>1,3</sup>, MD, Paola Pricolo<sup>4</sup>,  
18 MD, Sarah Alessi<sup>4</sup>, MD, Giuseppe Petralia<sup>3,4</sup>, MD, Francesco Alessandro Mistretta<sup>3,6</sup>, MD, Raffaella  
19 Cambria<sup>5</sup>, MSC, Federica Cattani<sup>5</sup>, MSC, Ottavio De Cobelli<sup>3,6</sup>, PROF, Roberto Orecchia<sup>7</sup>, PROF, Barbara  
20 Alicja Jereczek-Fossa<sup>1,3</sup> PROF  
21  
22  
23  
24  
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26  
27  
28  
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31 **Affiliations:**

- 32  
33  
34  
35  
36 1. Division of Radiotherapy, IEO, European Institute of Oncology IRCCS, Via Ripamonti 435, 20141,  
37 Milan, Italy  
38  
39 2. Molecular and Pharmaco-Epidemiology Unit, Department of Experimental Oncology, IEO,  
40 European Institute of Oncology IRCCS, Via Ripamonti 435, 20141, Milan, Italy  
41  
42 3. Department of Oncology and Hemato-Oncology, University of Milan, Via Festa del Perdono 7,  
43 20122, Milan, Italy  
44  
45 4. Division of Radiology, IEO, European Institute of Oncology IRCCS, Via Ripamonti 435, 20141,  
46 Milan, Italy  
47  
48 5. Medical Physics Unit, IEO, European Institute of Oncology IRCCS, Via Ripamonti 435, 20141,  
49 Milan, Italy  
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6. Division of Urology, IEO, European Institute of Oncology IRCCS, Via Ripamonti 435, 20141,  
Milan, Italy

7. Scientific Directorate, IEO, European Institute of Oncology IRCCS, Via Ripamonti 435, 20141,  
Milan, Italy

\* Equally contributed

§ Corresponding author:

Giulia Marvaso

Division of Radiotherapy

IEO European Institute of Oncology IRCCS

Via Ripamonti 435, 20141, Milan

e-mail: [giulia.marvaso@ieo.it](mailto:giulia.marvaso@ieo.it)

Keywords: prostate cancer; extreme hypofractionation; dominant intraprostatic lesion; quality of life;  
clinical trial;

## **DECLARATIONS**

## **FUNDING**

None

## **CONFLICT OF INTEREST**

All the authors declare that they do not have any conflicts of interest.

## **COMPLIANCE WITH ETHICAL STANDARDS**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. In this research, no animals were involved. All patients signed a written informed consent for radiation therapy and written informed consent for the use of the anonymized data for research or educational purpose.

1 The present study has been reviewed and approved by the Internal Review Board of the Division of  
2 Radiotherapy, IEO, European Institute of Oncology IRCCS, Via Ripamonti 435, 20141, Milan, Italy.  
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5

## 6 **AUTHORS CONTRIBUTION**

7  
8 GM and BAJF were responsible for the study conception and design, and had final responsibility for the  
9 decision to submit the manuscript for publication. GM, SGG, FB and SG drafted the manuscript. GM, GC,  
10 SV, DPR, GR, DZ, CIF, ELR, PP, SA, GP, FAM, RC and FC were responsible for acquisition and analysis of  
11 data. GM, SGG, FB, SG and BAJF were responsible for interpretation of data. MP, ODC, RO and BAJF  
12 substantially revised the work. All authors have read and approved the final version of the manuscript  
13 and have agreed both to be personally accountable for the author's own contributions and to ensure  
14 that questions related to the accuracy or integrity of any part of the work, even ones in which the author  
15 was not personally involved, are appropriately investigated, resolved, and the resolution documented  
16 in the literature.  
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## 30 **ACKNOWLEDGMENTS**

31 SGG was partially supported by Associazione Italiana per la Ricerca sul Cancro (AIRC), by project IG-  
32 14300 "Carbon ions boost followed by pelvic photon intensity modulated radiotherapy for high-risk  
33 prostate cancer", registered at ClinicalTrials.gov (NCT02672449). The study was also supported by  
34 project IG-13218 "Short-term High Precision Radiotherapy for Early Prostate Cancer With Concomitant  
35 Boost on the Dominant Lesion", registered at ClinicalTrials.gov (NCT01913717). The sponsors did not  
36 play any role in the study design, collection, analysis and interpretation of data, nor in the writing of the  
37 manuscript, nor in the decision to submit the manuscript for publication  
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## 58 **ABSTRACT**

## Purpose/Objective

As part of the AIRC IG-13218 (NCT01913717), we analyzed data from patients with low and intermediate risk prostate cancer treated with extreme hypofractionated radiotherapy (RT) and simultaneous boost on the intraprostatic lesion. The aim of the study is to identify clinically meaningful information through the analysis of validated questionnaires testing gastrointestinal (GI) and genitourinary (GU) RT related toxicity and their impact on quality of life (QoL).

## Material/methods

At the end of RT treatment, clinical assessment and prostate-specific antigen (PSA) measurements were performed every 3 months for at least 2 years and GI and GU toxicities were evaluated contextually. QoL of enrolled patients was assessed by International Prostatic Symptoms Score (IPSS), Quality Life Questionnaire - Core 30 (QLQ-C30), QLQ prostate specific (QLQ-PR25) and sexual activity by International Index of Erectile Function (IIEF-5). Patients score changes were calculated at the end of RT, at one month after RT and at 12 and 24 months.

## Results

Sixty-five prospectively enrolled patients were analyzed. Extensive analysis of different QoL assessments showed that patients' tolerance was satisfactory across all the considered time points, with no statistically significant change of QoL from baseline compared to that before RT. Overall survival and biochemical progression-free survival at 2-years were of 98% and 97%, respectively.

## Conclusion

Although the low toxicity of extreme hypofractionation and the encouraging tumor outcome, a longer follow up is necessary to confirm these findings. The increasing dose to the dominant intraprostatic lesion does not worsen the RT toxicity and consequently does not affect patients' QoL, thus questioning the possibility of an even more escalated treatment.

## 1. INTRODUCTION

1  
2 Radiation therapy (RT) represents a curative-intent treatment option in the management of localized  
3 prostate cancer (PCa), with disease progression and cancer-specific death rates comparable to radical  
4 surgery [1,2]. In the last three decades, starting from the radiobiological rationale of a low  $\alpha/\beta$  ratio in  
5 PCa [3] and the technological advancement in treatment delivery (image-guidance RT, IGRT, intensity-  
6 modulated RT, IMRT, and stereotactic body RT, SBRT), multiple clinical trials on moderate  
7 hypofractionation have shown the effectiveness and the safety of this treatment [4-11], both in terms of  
8 oncological outcomes and toxicity profile [5,12-15].

9  
10 Recent evidence suggest that at least non-inferior outcomes would be achievable also with extremely  
11 hypofractionated regimens, defined as the delivery of 5-10 Gy/fraction in 4-7 fractions [11,16-19].

12  
13 Based on these encouraging results, three extremely hypofractionated schedules (36.25 Gy at 7.25  
14 Gy/fraction, 37 Gy at 7.4 Gy/fraction and 40 Gy at 8.0 Gy/fraction) have been included in the last  
15 versions of the National Comprehensive Cancer Network (NCCN) guidelines as Level 2A treatment  
16 options for PCa patients staged from very low to favorable intermediate risk group [20]. In this setting,  
17 new schedules include simultaneous integrated boost (SIB) to the dominant intraprostatic lesion (DIL)  
18 [21]. However, with the aim of insuring precise and safe treatment, this option require steep dose  
19 gradients and the use of multiparametric resonance (mpMRI) imaging [22].

20  
21 Increasing focus to patients' reported outcomes (PROs) is reserved to several medical fields [23]. In the  
22 current setting, the availability of multiple treatment options, as well as the slow-progressive course of  
23 the disease, suggest that PROs may be useful for the decisional process. Although patients' satisfaction  
24 is generally high at the end of treatment [24,25], multiple psychological and physical long-term side  
25 effects are emerging, ranging from treatment-related symptoms to fatigue and major depressive  
26 disorders [26,27]. Furthermore, a consistent underestimation of side effects severity by physician has  
27 been recognized [27,28], highlighting the need for a more comprehensive assessment in every-day  
28 clinical practice. The systematic use of validated questionnaires for quality of life (QoL) would allow to  
29 improve personalized treatments and therapeutic index for PCa.

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1 This is specifically true for the recently introduced extreme hypofractionation: accurate side effects  
2 evaluation and longer follow-up periods are warranted in order to fully assess chronic treatment-  
3 related comorbidities and endorse its safety in clinical practice.  
4

5  
6 Based on these premises, in the context of the prospective phase II study “Short-term high precision  
7 radiotherapy for early prostate cancer with concomitant boost to the dominant lesion, AIRC-IG-13218”  
8  
9 we analyzed data of a cohort of PCa patients treated with extreme hypofractionation, aiming to evaluate  
10  
11 gastrointestinal (GI) and genitourinary (GU) RT related toxicity and its impact on QoL.  
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## 19 **2. MATERIALS AND METHODS**

### 20 **2.1 Patient cohort**

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23 Between October 2014 and January 2018, a prospective series of patients diagnosed with low and  
24  
25 intermediate risk PCa were enrolled in this study and treated with extreme hypofractionated RT at the  
26  
27 Division of Radiation Oncology in European Institute of Oncology (IEO). The inclusion and exclusion  
28  
29 criteria along RT treatment details and study design of this phase II prospective trial are described in  
30  
31 the previously published protocol [29], registered at ClinicalTrials.gov as NCT01913717, and first  
32  
33 results have already been reported [30].  
34  
35

36  
37 This trial had been approved by the Ethics Committee of the IEO and Centro Cardiologico Monzino of  
38  
39 Milan IEOS768/113. All patients signed a dedicated Informed Consent before admission.  
40

41  
42 For each patient, baseline information, clinical characteristics, pre-treatment mpMRI and uroflowmetry  
43  
44 data were collected.  
45

### 46 **2.2 Radiation therapy treatment planning and delivery**

47  
48  
49 Computed tomography (CT) simulation, volume of interest contouring, and treatment delivery were  
50  
51 performed following the previously described methodology [29].  
52

53  
54 Briefly, to assure an accurate image registration, a pelvic multiparametric magnetic resonance (mpMRI)  
55  
56 was performed before CT treatment simulation for each patient in the same treatment position [31,32].  
57

58  
59 The clinical target volume (CTV) was represented by the whole prostate. A margin of 3 mm posteriorly  
60  
61 and 5 mm in all other directions was added to create the prostate planning target volume (PTV) and 3  
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1 mm in all directions for the DIL. We delineated as Organ at Risk (OARs) the following structures: urinary  
2 bladder, rectum, posterior rectal wall, anal canal, urethra, peritoneal cavity/bowel bag, penile bulb,  
3  
4 penis, testis, femoral heads and necks, and cauda equina.  
5

6 The whole prostate received a dose of 36.25 Gy in 5 fractions (7.25 Gy/fraction), corresponding to 90.6  
7  
8 Gy in 45 fractions according to the linear quadratic model, assuming  $\alpha/\beta = 1.5$  Gy for PCa. The DIL  
9 received a SIB of 37.5 Gy in 5 fractions (7.5 Gy/fraction), equivalent to 96.4 Gy with conventional  
10  
11 fractionation. The treatment was delivered every other day.  
12  
13

14 Patients were trained to present for access to RT with an empty rectum and full bladder and the IGRT  
15  
16 was used to localize the target volume. The use of  $\alpha$ -1 blockers and low doses of steroids were  
17  
18 recommended to lower the risk of urinary obstruction and minimize inflammatory effects.  
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### 22 23 **2.3 Treatment assessment of QoL and follow-up**

24  
25 Clinical assessment and prostate-specific antigen (PSA) measurements were performed at the end of RT  
26  
27 treatment and afterwards every 3 months for at least 2 years.  
28

29 GI and GU toxicities were scored according to Radiation Therapy Oncology Group and European  
30  
31 Organization for Research and Treatment of Cancer (RTOG/EORTC) scoring criteria [33] and registered  
32  
33 as the maximum toxicity observed during the follow-up.  
34  
35

36 QoL of enrolled patients was assessed by the IPSS, Quality Life Questionnaire - Core 30 (QLQ-C30),  
37  
38

39 QLQ prostate specific (QLQ-PR25) and sexual activity by the International Index of Erectile Function  
40  
41 (IIEF-5).  
42

43 The IPSS is based on seven questions about urinary symptoms and one question concerning QoL. Each  
44  
45 question can be answered with a 0 to 5 score. The total score can therefore range from 0 to 35  
46  
47 (asymptomatic to very symptomatic).  
48  
49

50 The QLQ-C30 contains scales and items addressing functional aspects, symptoms and QoL evaluations  
51  
52 of cancer patients.  
53

54 The QLQ-PR25 is a questionnaire regarding urinary, gastrointestinal, sexual, treatment-related  
55  
56 symptoms to be used in conjunction with the QLQ-C30 for assessing the QoL of PCa patients varying in  
57  
58 disease stage and treatment modality (i.e. surgery, chemotherapy, RT, etc.).  
59  
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61



1 The IIEF-5 is a 5-item questionnaire, developed to diagnose the severity of erectile dysfunction. It ranges  
2 from 0 to 25, with higher scores describing better sexual functioning.

3  
4 IPSS, QLQ-C30, QLQ-PR25 and the IIEF-5 questionnaires were administered following these time points:  
5  
6 at baseline, at the end of RT, at one month after RT and at 12 ad 24 months. IPSS at 6 month and at 24  
7  
8 months were not considered during the analysis due to the large amount of missing values.  
9

## 10 11 **2.4 Oncological outcomes**

12  
13 Oncological outcomes were evaluated in terms of biochemical response, time to biochemical failure and  
14  
15 overall survival (OS). Biochemical response was assessed through trimestral PSA evaluation. OS was  
16  
17 defined as the time interval between the date of RT beginning and death from any cause. For patients  
18  
19 lost to follow-up, information on vital status was obtained through municipal vital statistics offices. Time  
20  
21 to biochemical failure was defined according to the Phoenix criterion (nadir PSA + 2 ng/mL).  
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## 26 **2.5. Statistical analysis**

27  
28 Categorical variables were reported as frequencies (percentages), whereas continuous variables were  
29  
30 summarized with the median value and interquartile range (25th-75th percentiles). We evaluated time  
31  
32 trends of (i) acute GI toxicity and GU toxicity; and (ii) IPSS, QLQ-C30, QLQ-PR25 and the IIEF-5  
33  
34 questionnaires.  
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37  
38 The missing IPSS scores at baseline were replaced by those obtained after RT (where available) and vice  
39  
40 versa.  
41

42  
43 Multivariate logistic regression models with generalized estimation method (GEE) were used to test the  
44  
45 association between bladder volume and GU toxicity  $\geq$  Grade (G) 1 over time. Predicted values of toxicity  
46  
47 were plotted against rectum volume and bladder volume for each time point.  
48

49  
50 Assuming that missing IPSS values were missing at random (MAR), a multivariate linear mixed effects  
51  
52 model for repeated measures was adopted to study the trend of change of IPSS from baseline. Residuals  
53  
54 from full models were checked to assess normal distribution.  
55

56  
57 All scales of QLQ-C30 (functioning scales: Physical Functioning, Role Functioning, Emotional  
58  
59 Functioning, Cognitive Functioning, Social Functioning; general health status scale: Global health status  
60  
61 / QoL; symptom scales: Fatigue, Nausea/Vomiting, Pain, Dyspnea, Insomnia, Appetite loss, Constipation,  
62  
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Diarrhea, Financial Problems) were built according to the EORTC manual and transformed to 0-100 scales, with higher scores reflecting either more symptoms or higher levels of functioning or QoL.

Four multi-item scales (Urinary symptoms, Bowel symptoms, Hormonal treatment-related symptoms, Sexual activity), a single-item scale (Bother due to the use of incontinence aid) and a conditional multi-item scale were obtained from the questionnaire QLQ-PR25. All scales were built following the EORTC guidelines, except for the Sexual activity and the Sexual functioning scales: Question 50, 51 and 52 were reversed so that higher scores identify better sexual conditions. All raw QLQ-PR25 scores were transformed to 0-100 scales.

For both QLQ-C30 and QLQ-PR25 imputation of missing answers was performed as following: if a patient answered less than half the questions in a scale, the scale was considered to be missing; if a patient answered at least half of the questions in a scale, the average score of the answered questions was calculated and imputed as the response to questions which had not been answered.

Within-patient score changes of IPSS, and every scale of QLQ-C30, QLQ-PR25 and IIEF-5 questionnaires were calculated at each time point from baseline. Linear mixed models for repeated measures were used to detect a trend in the changes. The same analyses were repeated stratifying the patients according to the median value of the bladder volume (<341 cm<sup>3</sup> vs. ≥341 cm<sup>3</sup>). All estimates were adjusted for the baseline score. Residuals from full models were checked to assess normal distribution.

A two-sided p-value <0.05 was considered significant for all statistical analyses.

The analyses were performed using SAS software (SAS Institute Inc., Cary, USA), version 9.4 and R software (<http://www.Rproject.org>), version 3.5.2.

### 3. RESULTS

#### 3.1 Study population

Sixty-five patients were consecutively enrolled in this trial. Their characteristics at baseline are summarized in **Table S1 - Supplementary Materials**. Patients' response rates are reported from **Table S2 to Table S8 – Supplementary Materials**.

#### 3.2 Toxicity assessment

1 Physician-rated GU and GI toxicities at the end of treatment, at 1 months and over 6 months after the  
2 end of RT are reported in **Table 1**. Overall, patients' tolerance was assessed as satisfactory across all the  
3 considered time points, with no residual toxicity exceeding G2 at 6 months after the end of treatment,  
4 except for one patient who developed G3 GI symptoms during the course of follow-up. Urinary function  
5 as assessed by IPSS showed a statistically significant variation from baseline ( $p=.002$ ), despite missing  
6 data during the follow-up. Specifically, 63/65 (97%) patients fulfilled the IPSS questionnaire at baseline  
7 and at the end of RT, 59/65 (91%) at 1 month and 48/65 (74%) at 12 months. The most relevant  
8 deterioration in IPSS from baseline was reported after 1 month from the end of treatment, although a  
9 sizable recovery towards baseline value was assessed at 12 months ( $p=0.05$ ). Boxplots reporting IPSS  
10 modification are shown in **Figure 1**.

11 The QLQ-PR25 Urinary Symptoms score was also analyzed to evaluate the urinary function. A  
12 deterioration of symptoms from baseline was observed already at the end of RT and maintained at one  
13 month after, with a recovery towards baseline value at 12 months (**Figure S1 – Supplementary**  
14 **Materials**). Although statistical significance was not reached ( $p=0.51$ ), these results are consistent with  
15 those obtained from IPSS analysis. Interestingly, different trends of urinary symptoms can be found if  
16 patients are stratified according to the median bladder volume ( $341 \text{ cm}^3$ ): patients with a volume  $<$   
17 median showed a worsening of symptoms after RT that was kept changeless throughout the entire  
18 follow-up ( $p=0.42$ ). On the contrary, patients with volume  $\geq$  than the median reported a significant  
19 decreasing trend of deterioration of symptoms with a median complete recovery at 12 months (**Figure**  
20 **S2 – Supplementary Materials**).

### 21 **3.3 Bladder and Rectal volumes correlation with GU and GI Toxicity**

22 **Genitourinary Toxicity.** There was no evidence that bladder volume and physician-rated GU toxicity  
23  $\geq$ G1 are associated ( $p=.60$ , Figure S2 – Supplementary Materials). Conversely, significant decreasing  
24 probability of toxicity ( $G>1$ ) along time points ( $P=.02$ ) were found.

25 **Figure 2** shows that patients with a bladder volume greater than its median value ( $341 \text{ cm}^3$ )  
26 experienced a more relevant deterioration in IPSS score as compared to baseline at 1 month following

1 the end of RT (median IPSS = 1.5, IQR (-1, 8)) Nevertheless, bladder volume seems not to affect IPSS at  
2 12-months follow-up (p=.24).  
3

4 **Gastro-intestinal Toxicity.** Patients' probability of experiencing a GI physician-rated toxicity  $\geq$  G1 was  
5 found to be correlated with rectal volume measured on planning CT scan (p=.05). Predicted value of  
6 rectal volume was more relevant at 1-month after the end of treatment and significantly decreases over  
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11 6 months after treatment completion (p=.03) (**Figure 3**).  
12

### 13 **3.4 Quality of Life**

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16 Although there was no statistical evidence of changes in Quality of life along time, a trend towards  
17 amelioration of QLQ-C30 Global Health Status/QoL was however found, with minimum values being  
18 recorded at the end of treatment and at 1 month from its completion, and a recovery to pre-RT values  
19  
20  
21 at one year (**Figure 4**). Again, although no significant, an improvement from baseline of QLQ-C30  
22  
23 Emotional Functioning Score was noted already one month after RT and was maintained at the 12-  
24  
25 months follow-up (p=.85), whereas the change of QLQ-C30 Fatigue score showed a trend towards  
26  
27  
28 deterioration over time (p= .11) (**Figure 4**).  
29  
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31

### 32 **3.5 Sexual function assessment**

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35 According to the QLQ-PR25 questionnaire, sexual activity changed over time after RT (p=.05). Although  
36  
37 no change in sexual activity was found right after RT, a median worsening of condition from baseline  
38  
39 occurred in patients after 1 month, followed by a trend of improvement that led to a considerable  
40  
41 recovery at the 12-months follow-up (**Figure 5a**). Conversely, a trend of deterioration of Sexual  
42  
43 Functioning was found in patients sexually active patients, which started 1 month after the end of RT  
44  
45 and was maintained at the 12-months evaluation (**Figure 5b**).  
46  
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48  
49 The analysis of IIEF-5 did not show any significant change of erectile function from baseline (p=.46),  
50  
51 although a slight worsening of function was assessed after 1 month from the end of RT, as reported in  
52  
53 **Figure 5c**.  
54

### 55 **3.5 Oncological outcomes**

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58 Because at present follow-up is insufficient to investigate primary endpoint, the current study reports  
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60 findings about treatment-related toxicity within 2 years.  
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1 The median PSA before the beginning of treatment was 6.07 ng/ml and quickly decreased within the  
2 first 3 months after RT, reaching a median value of 2.20 ng/ml. After 3 months, the PSA kept steadily  
3 decreasing, with a median PSA of 0.49 ng/ml at 21-24 months after treatment (**Figure S3 -**  
4  
5  
6 **Supplementary Materials**). Although patients with intermediate risk had higher median PSA at  
7  
8 baseline (6.07 ng/ml) than patients with low risk (5.30 ng/ml), they had a faster decrease of PSA within  
9  
10 the first 6 months after RT that led to smaller median values of PSA throughout the follow-up (**Figure**  
11  
12 **S3 - Supplementary Materials**).

13  
14  
15  
16 Only one patients out of the 65 ones died (for a cause not related to the disease ), leading to an OS of  
17  
18 98% at 2-years.

19  
20 Biochemical progression-free survival (b-PFS) at 2-years was of 97%. Since 2014, only 2 patients  
21  
22 experienced biochemical and clinical relapse. Subsequently to primary RT PSA decreased , but after 3  
23  
24 years a progressive increase was noted until trespassing the biochemical relapse. As a result, both  
25  
26 patients underwent a Choline PET and a prostate MRI, which showed a clinical relapse on DIL treated  
27  
28 with RT. Considering the local relapse of PCa, patients underwent partial prostate re-irradiation with a  
29  
30 schedule of 35 Gy in 5 fractions. Treatment was well tolerated and patients are actually in follow up.  
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1 fractions or 62 Gy in 20 fractions) or SBRT (36.35 Gy in 5 fractions). G2 or worse toxicity was not  
2 significantly different for GI events (12.1% in the standard arm vs 10.1% in the SBRT arm), nor GU  
3 events (27.2% in the standard arm vs 23.2% in the SBRT arm). In addition, in this case, there was no  
4 difference between the two groups of patients and less than 1% of patients developed G3 toxicity [35].  
5  
6 The phase III trial HYPO-RT-PC demonstrated the non-inferiority of ultra-hypofractionated RT [36].  
7  
8 Patients affected by intermediate/high risk PCa were randomized to receive either 78 Gy in 39  
9 fractions/daily or 42.7 Gy in 7 fractions every other day. Both arms showed similar late adverse events,  
10 except higher GU at 1 year in the experimental arm (32 [6%] of 528 patients vs 13 [2%] of 529 patients).  
11  
12 At 5 years-follow-up the frequency of G2 or worse toxicity was 5% in both arms.  
13  
14 Regarding PROs, it is well known that, preserving QoL is of high importance for many patients; for  
15 instance, previous studies have demonstrated that >50% of men consider the preservation of sexual  
16 function to be important [36-39]. QoL and toxicities outcomes are widely taken in considerations by  
17 many trials [36, 41-43] and studies [44-46] in the context of hypofractionation, including MR-linac  
18 approach, showed results comparable to the ones of the present study. Our results showed no statistical  
19 worsening with respect to the initial condition assessing the safety of such ultra-hypofractionated  
20 treatments.  
21  
22 Regarding our data, we have acquired pre-treatment data for all IPSS, QLQ-C30 and QLQ-PR25  
23 questionnaires. This allowed us to analyze changes since from baseline. Similar findings were reported  
24 from the previously mentioned studies [36,40], in which physician-recorded and patient-reported  
25 treatment-related late side-effects of ultra-hypofractionation are similar to those of conventional  
26 fractionation.  
27  
28 Despite the promising results, our prospective study showed intrinsic limitations. The low number of  
29 subjects prevented us from finding significant differences between the groups compared. It is worth to  
30 mention that we tried to moderate the effects of missing questionnaire scores by replacing them with  
31 other from different time points. In addition, the short median follow-up makes the results for tumor  
32 outcome less reliable compared with those for toxicity.  
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### 3. CONCLUSIONS

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2 Our data showed that QoL of patients treated with extreme hypofractionation with a dose escalation to  
3  
4 the DIL remains acceptable mainly because the related GI and GU toxicities were really low.  
5

6  
7 The toxicity is in line with historical cohorts, therefore SBRT+DIL vs standard of care in a randomised  
8  
9 trial should be considered. In addition, although tumor outcomes are encouraging, longer follow up is  
10  
11 warranted to confirm these findings.  
12  
13

#### 14 15 16 17 **Declarations**

#### 18 19 **FUNDING**

20  
21 SGG was partially supported by Associazione Italiana per la Ricerca sul Cancro (AIRC), by project IG-  
22  
23 14300 “Carbon ions boost followed by pelvic photon intensity modulated radiotherapy for high-risk  
24  
25 prostate cancer”, registered at ClinicalTrials.gov (NCT02672449). The study was also supported by  
26  
27 project IG-13218 “Short-term High Precision Radiotherapy for Early Prostate Cancer With Concomitant  
28  
29 Boost on the Dominant Lesion”, registered at ClinicalTrials.gov (NCT01913717). The sponsors did not  
30  
31 play any role in the study design, collection, analysis and interpretation of data, nor in the writing of the  
32  
33 manuscript, nor in the decision to submit the manuscript for publication  
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#### 40 **CONFLICT OF INTEREST**

41  
42 All the authors declare that they do not have any conflicts of interest.  
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#### 47 **COMPLIANCE WITH ETHICAL STANDARDS**

48  
49 All procedures performed in studies involving human participants were in accordance with the ethical  
50  
51 standards of the institutional and/or national research committee and with the 1964 Helsinki  
52  
53 declaration and its later amendments or comparable ethical standards. In this research, no animals were  
54  
55 involved. All patients signed a written informed consent for radiation therapy and written informed  
56  
57 consent for the use of the anonymized data for research or educational purpose.  
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1 The present study has been reviewed and approved by the Internal Review Board of the  
2 Division of Radiotherapy, IEO, European Institute of Oncology IRCCS, Via Ripamonti 435,  
3 20141, Milan, Italy.  
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5

#### 6 **AUTHORS CONTRIBUTION**

7  
8  
9 GM and BAJF were responsible for the study conception and design, and had final responsibility for the  
10 decision to submit the manuscript for publication. GM, SGG, FB and SG drafted the manuscript. GM, GC,  
11 SV, DPR, GR, DZ, CIF, ELR, PP, SA, GP, FAM, RC and FC were responsible for acquisition and analysis of  
12 data. GM, SGG, FB, SG and BAJF were responsible for interpretation of data. MP, ODC, RO and BAJF  
13 substantially revised the work. All authors have read and approved the final version of the manuscript  
14 and have agreed both to be personally accountable for the author's own contributions and to ensure  
15 that questions related to the accuracy or integrity of any part of the work, even ones in which the author  
16 was not personally involved, are appropriately investigated, resolved, and the resolution documented  
17 in the literature.  
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#### 31 **PRECIS**

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33 The hypofractionation with the boost is feasible and could offer good clinical outcome. The related GI  
34 and GU toxicity do not significantly affect quality of life of the patients at 2-years of follow up.  
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41 Text pages: 20

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43 Tables: 2

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45 Figures: 6

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47 Supporting files: 1  
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## LIST OF TABLES AND FIGURES

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**Table 1.** Descriptive statistics of toxicity by grade and time.

**Figure 1.** IPSS score by time and from Baseline.

**Figure 2.** Change of IPSS score from Baseline grouped by Bladder Volume.

**Figure 3.** Predicted toxicity  $G \geq$  from multivariate logistic models by rectum volumes.

**Figure 4.** Change of QLQ-C30 from Baseline.

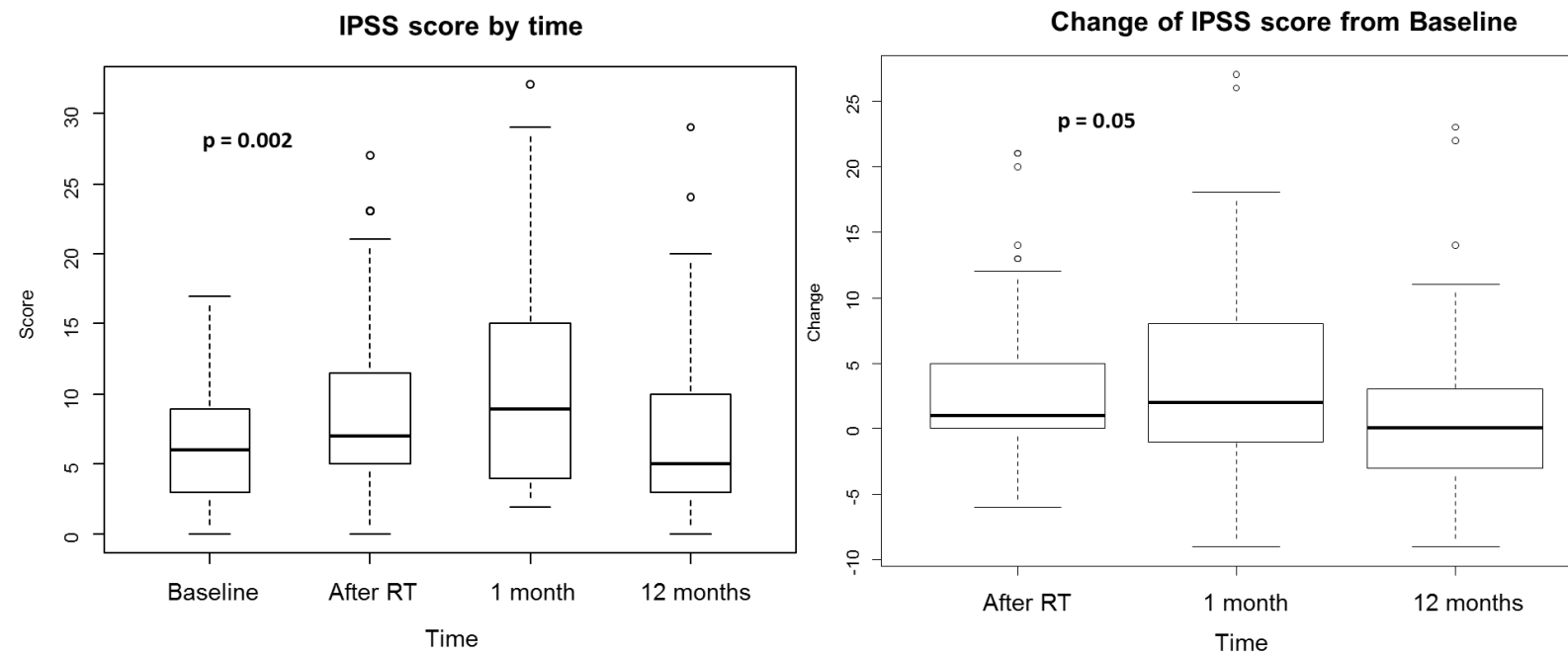
**Figure 5.** PR25 and IIEF-5 sexual activity and functions scores.

## LIST OF ABBREVIATION IN MANUSCRIPT, TABLES AND FIGURES

Abbreviation	Description
AIRC	Associazione Italiana per la Ricerca sul Cancro
BED	Biologically Effective Dose
b-PFS	Biochemical Progression-Free Survival
DIL	Dominant Intraprostatic Lesion
EBRT	External Beam Radiotherapy
GEE	Generalized Estimation Method
GI	Gastrointestinal
GU	Genitourinary
IGRT	Image-Guided Radiation Therapy
IIEF-5	International Index of Erectile Function
IMRT	Intensity Modulated Radiotherapy
IPSS	International Prostatic Symptoms Score
MAR	Missing At Random
mpMRI	multi-Parametric Resonance Imaging
NCCN	National Comprehensive Cancer Network
OS	Overall Survival
PACE-B	Prostate Advances in Comparative Evidence-B
PCa	Prostate Cancer
PRO	Patient Reported Outcome
PSA	Prostate-Specific Antigen
QLQ-C30	Quality Life Questionnaire - Core 30
QLQ-PR25	Quality Life Questionnaire prostate specific
QoL	Quality of Life
RT	Radiotherapy

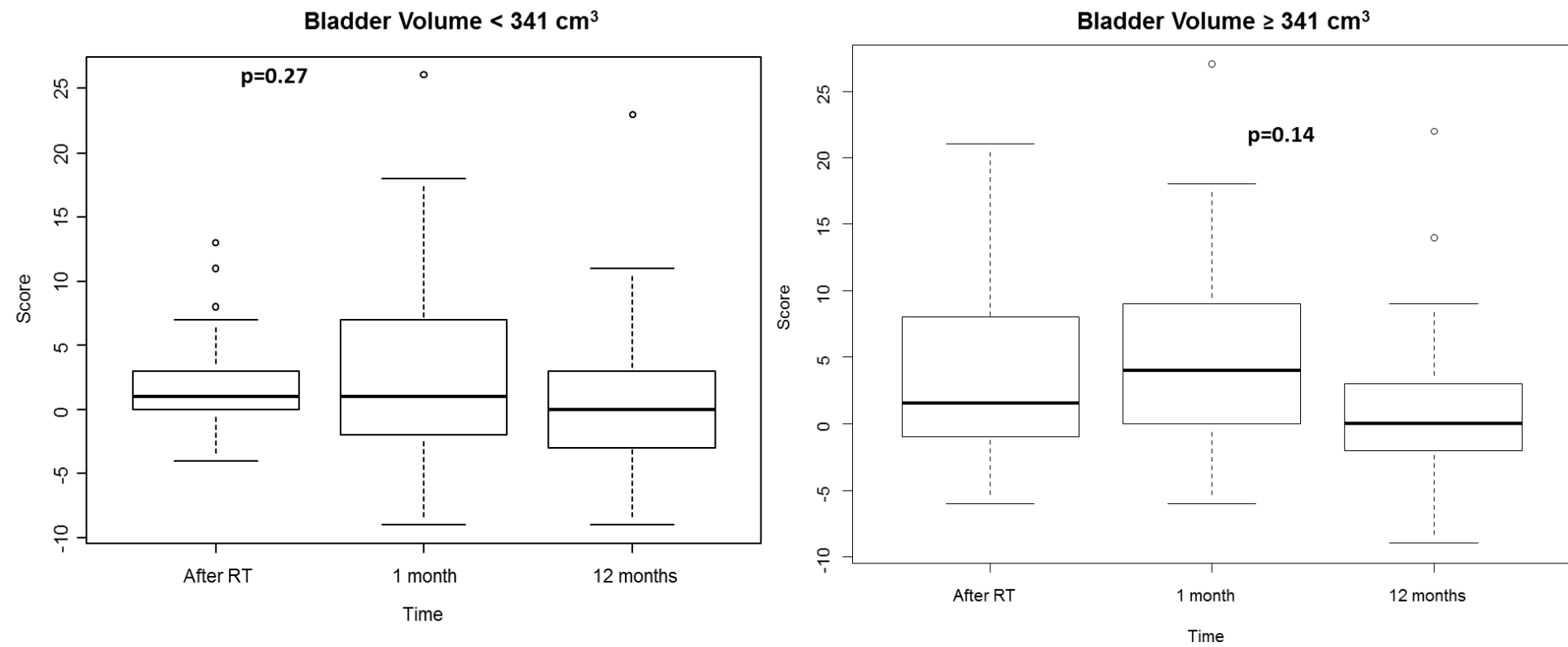


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2	SBRT	Stereotactic Beam Radiotherapy
3	SIB	Simultaneous Integrated Boost
4	VMAT	Volumetric Modulated Arc Therapy
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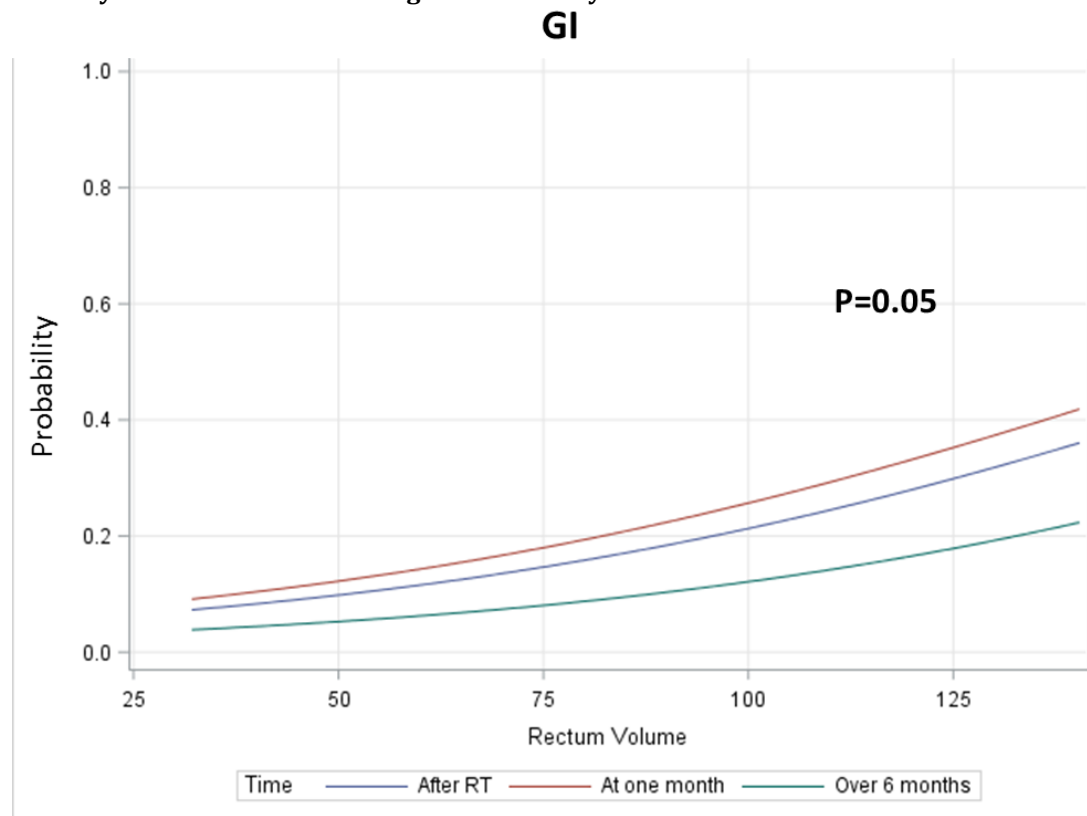
**Figure 1 - IPSS score by time and from Baseline.**

Legend: p-values are from linear mixed models for repeated measures evaluating, respectively, the effect of time on IPSS score and on IPSS change from bas



**Figure 2 – Change of IPSS score from Baseline grouped by Bladder Volume.**

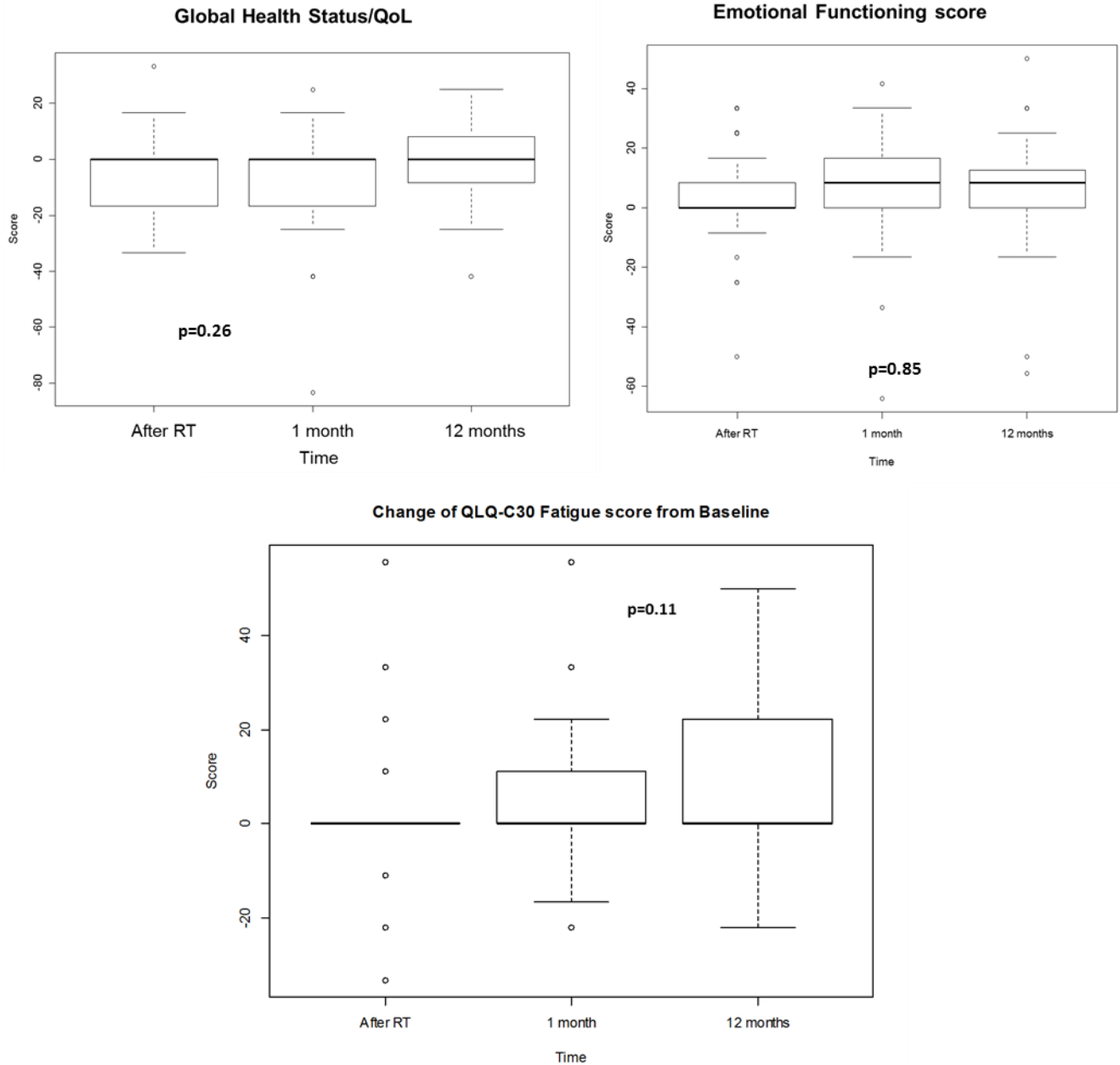
Legend: p-values are from linear mixed models for repeated measures evaluating the effect of time on the change of IPSS score from baseline stratified by median bladder volume.

**Figure 3 – Predicted toxicity  $G \geq$  from multivariate logistic models by rectum volumes.**

— After RT  
— At 1 month  
— Over 6 months

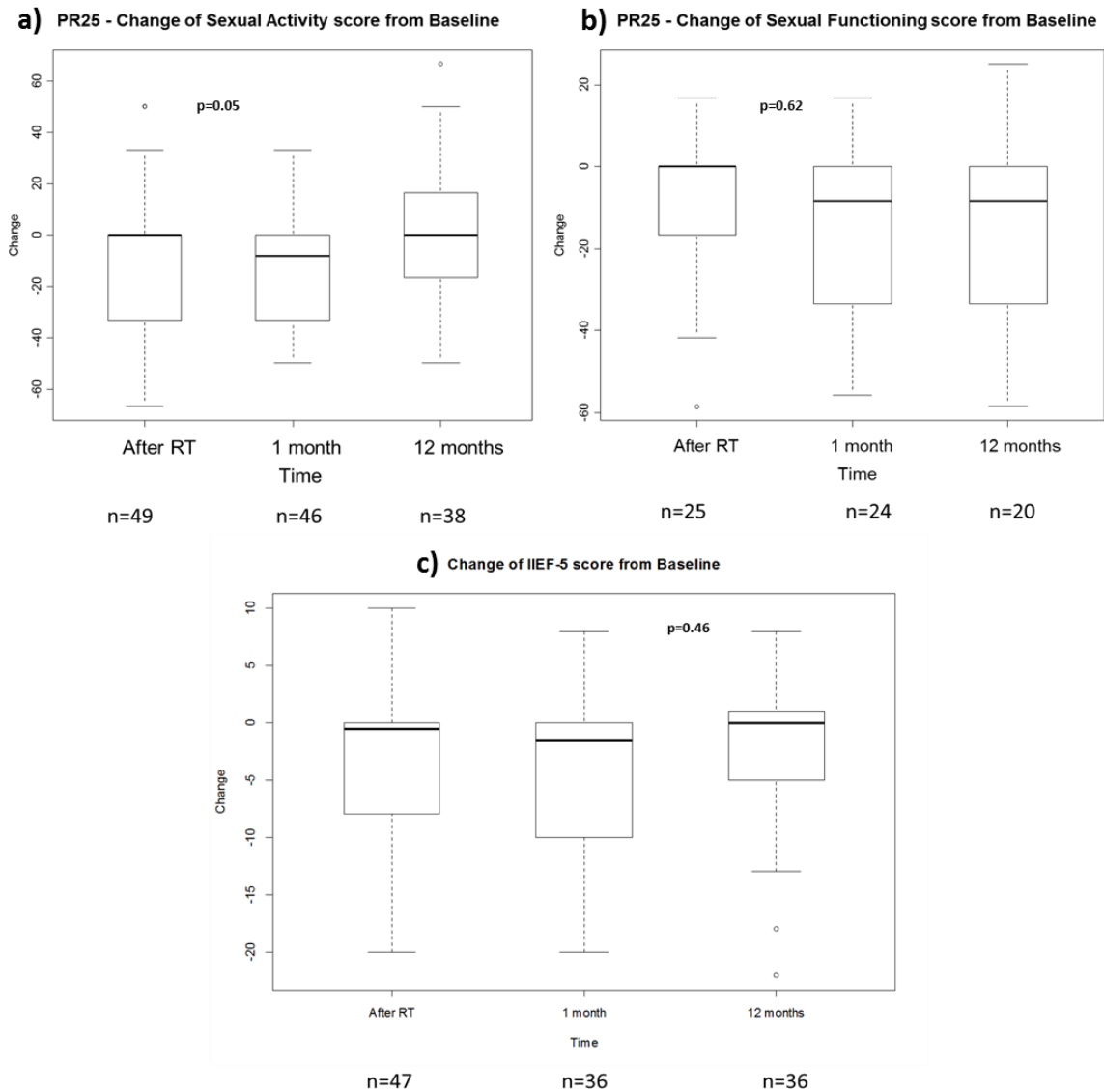
Legend: p-value is from a GEE model testing the association between rectum volume and GI toxicity  $\geq$  Grade (G) 1



**Figure 4- Change of QLQ-C30 from Baseline.**

Legend: p-values are from linear mixed models for repeated measures evaluating, respectively, the effect of time on the change of QoL score, Emotional Functioning score and Fatigue score from baseline.

**Figure 5 - PR25 and IIEF-5 sexual activity and functions scores.**



Legend: p-values are from linear mixed models for repeated measures evaluating, respectively, the effect of time on the change of Sexual Activity score, Sexual Functioning score and IIEF-5 score from baseline.

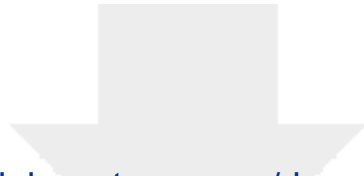


**Table 1 - Descriptive statistics of toxicity by grade and time.**

		<b>After RT</b>	<b>At 1 month</b>	<b>Over 6 months after RT*</b>
<b>GU toxicity,</b> n. (%)	Grade 0	38 (58.46)	42 (64.62)	48 (75.00)
	Grade 1	26 (40.00)	18 (27.69)	13 (20.31)
	Grade 2	1 (1.54)	4 (6.15)	3 (4.69)
	Grade 3	0 (0.00)	1 (1.54)	0 (0.00)
		<b>After RT</b>	<b>At 1 month</b>	<b>Over 6 months after RT*</b>
<b>GI toxicity,</b> n. (%)	Grade 0	56 (86.15)	54 (83.08)	59 (92.19)
	Grade 1	7 (10.77)	11 (16.92)	3 (4.69)
	Grade 2	2 (3.08)	0 (0.00)	1 (1.56)
	Grade 3	0 (0.00)	0 (0.00)	1 (1.56)

\*One patient has both late toxicities missing

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