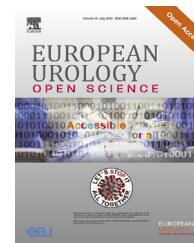


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## Voiding Dysfunction

# Multicentre International Study for the Prevention with iAluRil of Radio-induced Cystitis (MISTIC): A Randomised Controlled Study

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## Abstract

**Background:** Radiation-induced cystitis is a common side effect of radiotherapy (RT) to the pelvic area. Hyaluronic acid (HA) and chondroitin sulfate (CS) are components of the urothelial mucosa and positive results have been obtained for intravesical HA/CS instillations for the treatment of urinary tract infections and bladder pain syndrome. HA/CS may also have a protective effect against RT bladder toxicity.

**Objective:** To investigate whether HA and CS protect the urothelium during RT, alleviate lower urinary tract symptoms, and improve quality of life.

**Design, setting, and participants:** This multicentre randomised controlled trial was conducted across seven centres in four countries. Male patients aged  $\geq 18$  yr scheduled to undergo primary intensity-modulated radiotherapy for localised prostate cancer were enrolled.

**Intervention:** Patients were randomised to intravesical HA/CS plus an oral formulation of curcumin, quercetin, HA, and CS (group A) or no treatment (group B).

**Outcome measurements and statistical analysis:** The primary endpoint was absolute changes from baseline to follow-up in urinary domain scores for the Expanded Prostate Cancer Index Composite (EPIC), the International Consultation on Incontinence Questionnaire-Male Lower Urinary Tract Symptoms (ICIQ-MLUTS), and the EuroQol Group EQ-5D-5L questionnaire. Data analysis for efficacy and safety outcomes was performed using an intention-to-treat (ITT) approach; the ITT population was defined as all randomised patients.

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**Results and limitations:** Of 57 patients screened, 49 were enrolled and randomly assigned to either active treatment (group A,  $n = 25$ ) or the control (group B,  $n = 24$ ). Three patients in the control group withdrew after randomisation. Changes from baseline to 12 mo were worse in the control group for subtotal scores for urinary symptoms and impact of symptoms on quality of life and for the total score ( $p = 0.05$ ,  $p = 0.003$ , and  $p = 0.008$ , respectively). There was a significant time  $\times$  group interaction in favour of active treatment for the incontinence symptom score ( $p = 0.011$ ) and bother score ( $p = 0.017$ ). The absence of a sham procedure and/or placebo is the main limitation.

**Conclusions:** Our results suggest that intravesical HA/CS in combination with an oral formulation may reduce urinary symptoms and improve QoL at short-term (1 yr) follow-up.

**Patient summary:** We investigated whether hyaluronic acid (HA) and chondroitin sulfate (CS) have a protective effect against the bladder toxicity of radiotherapy for prostate cancer. HA/CS used for weekly bladder irrigation for 6 wk and given orally with curcumin and quercetin for 12 wk reduced urinary incontinence symptoms and bother measured at 1-year follow-up. This may hold promise as a preventive treatment if the results are confirmed in further trials.

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## 1. Introduction

Acute and late radiation-induced cystitis is a common side effect occurring in up to 25% of patients during and after pelvic organ cancer treatment with radiotherapy (RT) [1]. Radiation-induced bladder toxicity is characterised by early acute inflammation, sometimes haemorrhagic, that resolves in many patients, and late fibrosis with filling/voiding dysfunction that can occur months or years later. The acute and late clinical complaints of patients often resemble those for acute or chronic cystitis, such as bladder pain syndrome, and some patients may also experience gross haematuria, which further impacts quality of life (QoL) and may require invasive treatment [1–3].

Ionising radiation impacts cells, tissues, and pelvic organs of the body via different mechanisms and effects. In *in vivo* animal models, irradiated bladders exhibit oedema, inflammatory cell infiltrate, blood vessel dilation and urothelial loss, and exhibit fibrosis and disruption of the urothelial barrier [4]. The urothelial barrier consists of a protective mucin layer that contains negatively charged glycosaminoglycans, the main components of which are hyaluronic acid (HA) and chondroitin sulfate (CS) [5]. RT may impair the function of the urothelium because of fibrosis and nerve changes in bladder tissue, leading to an acute local inflammatory response and chronic lower urinary tract symptoms (LUTS), whether or not associated with gross haematuria and pain [6,7].

Several strategies have been used to treat radiation-induced cystitis [3,8,9]. However, with the possible exception of modest effects with hyperbaric oxygen, most of these treatments have failed to demonstrate optimal and long-term efficacy [1,10]. In 2019, the International Consultation on Incontinence Research Society identified gaps in the knowledge on effects of radiation on the lower urinary tract

and proposed several questions that remained to be addressed through further research [11].

Several clinical studies have shown the efficacy of intravesical instillation of high concentrations of sodium hyaluronate and sodium CS in protecting the urothelium in different settings [12–15]. Considering the positive results obtained for intravesical HA and CS instillation for the treatment of bladder diseases such as urinary tract infections and bladder pain syndrome, which symptomatically resemble radiation-induced cystitis, we reasoned that protection of the urothelium by HA and CS during RT could represent a preventive strategy capable of alleviating the consequences, hence avoiding or improving the symptoms of radiation-induced cystitis and improving QoL. Therefore, we tested the hypothesis that intravesical HA/CS (iAluRil) plus an oral formulation of HA, CS, curcumin, and quercetin (iAluRil Soft Gels) may prevent acute and late radiation-induced cystitis and improve quality of life.

## 2. Patients and methods

### 2.1. Study design

This was an investigator-initiated, European, unblinded, randomised controlled trial (active vs no additional treatment) conducted in seven centres in four countries (Italy, Slovakia, Spain, Turkey) in a selected population of men with prostate cancer who underwent RT: the Multicentre International Study for the Prevention with iAluRil of Radiation-induced Cystitis (MISTIC).

The study was approved by the medical research ethics board of each participating centre and was conducted in compliance with the International Conference on Harmonization/Good Clinical Practice guidelines, national laws, applicable regulatory requirements, and the ethical principles of the Declaration of Helsinki. Specifically, the study was approved by the Ethics Committees of Universidad Autónoma de Barcelona, Università Vita-Salute San Raffaele, Ospedali Careggi, the

University of Palermo, St. Cyril and Methodius University Hospital, Fakultná nemocnica s poliklinikou Prešov, and Istanbul University. The overall protocol is available on ClinicalTrials.gov (NCT03493997) and follows the CONSORT guidelines.

## 2.2. Participants

Male patients aged  $\geq 18$  yr who were scheduled to undergo primary intensity-modulated radiotherapy (IMRT) for localised prostate cancer were enrolled. All patients provided written informed consent. The participants did not enter the trial if any of the following applied: female; life expectancy of  $< 24$  mo; radiologically confirmed metastasis; documented urethral strictures; ongoing chemotherapy; previous brachytherapy; history of chemoradiotherapy for prostate cancer; previous treatment with bacillus Calmette-Guérin; postvoid residual volume  $> 200$  ml; bladder calculi; neurogenic bladder; lower urinary tract infection; unstable cardiovascular disease/congestive heart failure; current nitrate or anticoagulant use; clinically significant hepatobiliary or renal disease; history of significant central nervous system injuries within 6 mo; and any other significant disease or disorder that, in the opinion of the investigator, might either put the participant at risk because of participation in the trial or influence the result of the trial or the participant's ability to participate in the trial.

## 2.3. Randomisation and masking

The randomisation (1:1) was carried out according to a predefined, centre-specific randomisation list prepared using validated software (Random Allocation Software version 1.0.0; <https://doi.org/10.1186/1471-2288-4-26>) by the appointed personnel. Treatment was not masked.

## 2.4. Procedures

All patients received external beam RT (EBRT) for prostate cancer, delivered as IMRT using moderate hypofractionation with a simultaneous integrated boost, guided by fiducial intraprostatic markers according to the European Organisation for Research and Treatment of Cancer guidelines for primary prostate cancer RT, and lasting for 6 wk [16]. After completion of screening (visit 1), eligible patients were randomly assigned at a 1:1 ratio to receive either active treatment (group A) or standard care (group B). Patients in group A received a sterile solution containing sodium hyaluronate 1.6%, 800 mg/50 ml and sodium chondroitin sulfate 2%, 1 g/50 ml (HA-SC; iAluRil Prefill; IBSA, Lodi, Italy) via weekly intravesical instillation for 6 wk, plus an oral soft-gel formulation (iAluRil Soft Gels; IBSA) containing 200 mg of CS, 20 mg of HA, 200 mg of quercetin, and 100 mg of curcumin, one capsule twice a day for 12 wk. Intravesical HA/SC was instilled in the 24 h before every RT weekly session. Patients in group B did not receive any intravesical or oral treatment. All other treatments were allowed except those mentioned in the exclusion criteria.

Patients in both groups were followed up and assessed at 4 wk after the first instillation (during the RT treatment period; visit 2); at 6 wk (at the end of the RT period; visit 3); at 12 wk (6 wk after the end of RT; visit 4); and 1 yr after RT initiation (visit 5). During the planning of treatment, regimen and average dose to the whole bladder was recorded to assess the impact of EBRT on urinary symptoms.

## 2.5. Outcomes

The primary outcome was the absolute change from baseline to follow-up in the Expanded Prostate Cancer Index Composite (EPIC) urinary single and overall domain score, the International Consultation on

Incontinence Questionnaire-Male Lower Urinary Tract Symptoms (ICIQ-MLUTS) score, and the EuroQol Group EQ-5D-5L questionnaire score. The secondary outcome was the rate of patients who stopped treatment with intravesical or oral iAluRil because of intolerance or adverse events. Tolerability endpoints included the discontinuation rate, significant deviation from the study treatment protocol for Group A, and safety, defined as drug-related adverse reactions.

## 2.6. Statistical analysis

To calculate the sample size, the EPIC questionnaire was fixed as the reference and a power analysis was conducted to determine the number of participants needed to detect an absolute change of 15 points in the EPIC urinary domain total score between the first and last visit, given a standard deviation of 20 and correlation of 0.500 between observations for the same subject. A sample size of 21 subjects for each group achieved 80% power to detect this difference at a 0.05 significance level (PASS version 11.0.7; NCSS, Kaysville, UT, USA). Data analyses for both efficacy and safety outcomes were performed using an intention-to-treat (ITT) approach; the ITT population was defined as all randomised patients.

The Shapiro-Wilk test was used to assess the variables followed a normal distribution. The Mann-Whitney *U* test and Wilcoxon signed-rank test were used for comparisons of independent and paired data, respectively. Frequencies of qualitative variables were analysed using the  $\chi^2$  test with Yates' continuity correction or Fisher's exact test. Comparisons within and between groups over time were analysed using a mixed-model repeated-measures analysis of variance (RM-ANOVA), Mauchly's test of sphericity, and Levene's test for equality of variances were used to exclude any possible violation of ANOVA assumptions. Time (variable value at baseline and at each follow-up visit) and group (therapy arms) were considered as within-subjects and between-subject factors, respectively, with five time levels and two group levels. Time  $\times$  group interactions were also evaluated. All statistical analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). In all analyses, a two-sided *p* value  $< 0.05$  was considered statistically significant.

## 3. Results

Of 57 patients screened between January 2017 and December 2019, seven did not agree to participate and one opted for radical prostatectomy; finally, 49 were eligible for inclusion. After completion of baseline assessments (visit 1), 25 patients were randomly assigned to group A and 24 to the control group (group B; Fig. 1).

Patient demographics and disease characteristics were similar in both groups (Table 1). The two groups were also well balanced with regard to the RT received; there were no significant differences in the number of sessions, RT doses, or other RT parameters (Table 2).

Two patients in group B withdrew consent after randomisation, and one in group B was diagnosed with a new cancer and was ruled out. No patients withdrew from the study because of catheter discomfort, and none discontinued oral therapy because of side effects. All of the patients were evaluated after 1 yr.

There were no significant differences in EPIC urinary domain scores between the groups at baseline. When single items were considered, scores at 12 mo for EPIC item 5 ( $p = 0.012$ ) and item 7 ( $p = 0.033$ ) were significantly higher in group A than in group B. In group B, a significant

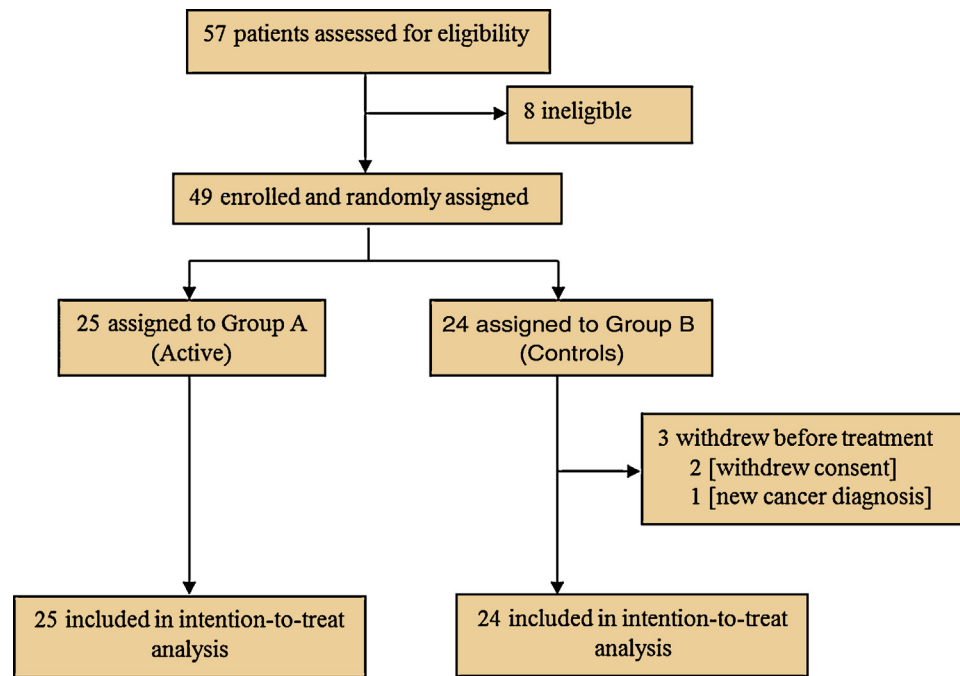


Fig. 1 – Flowchart of patient inclusion in the trial.

reduction was observed between baseline and last follow-up for item 1 ( $p = 0.021$ ), item 6 ( $p = 0.005$ ), and item 7 ( $p = 0.009$ ). The subtotal scores for the two main categories (urinary symptoms, items 1–5; and impact of symptoms on QoL, items 6–7) and for the total score (items 1–7) were significantly lower at 12 mo than at baseline in group B ( $p = 0.05$ ,  $p = 0.003$ , and  $p = 0.008$ , respectively). Changes in QoL items from baseline to the 12 mo significantly differed between groups A and B for item 6 ( $p = 0.002$ ), item 7 ( $p = 0.016$ ), the subtotal score for items 6–7 ( $p = 0.003$ ), and the overall score for items 1–7 ( $p = 0.006$ ). All data are reported in Table 3.

RM-ANOVA revealed statistically significant within-group factors over time for all questionnaire sections and a significant time  $\times$  group interaction for the items 6–7 subscore and the total score (items 1–7), with lower values in group B than in group A (Fig. 2).

There were no statistically significant differences at baseline for overall ICIQ-MLUTS scores evaluating male LUTS and impact on QoL (Table 4).

In group A, a statistically significant increase was observed between baseline and last follow-up for the total score ( $p = 0.019$ ) and voiding symptom score ( $p = 0.007$ ), while a significant increase was observed for the total score ( $p = 0.008$ ), incontinence symptoms score ( $p = 0.004$ ), and bother score ( $p < 0.0001$ ) in group B. Comparison of changes in incontinence score and bother score from baseline to last follow-up between the two groups revealed that the change in score was significantly greater (worse condition) in group B ( $p = 0.004$  and  $p < 0.0001$ , respectively). RM-ANOVA showed a statistically significant higher score over time for group B versus A for total score ( $p < 0.0001$ ), incontinence symptoms score ( $p = 0.002$ ), and bother score ( $p = 0.001$ ). There was a significant time  $\times$  group interaction for the incontinence

Table 1 – Baseline characteristics<sup>a</sup>

	Group A (n=25)	Group B (n=24)	p value
Median age, yr (IQR)	67 (64.5–75.5)	71 (68.5–74.5)	0.508
Median body mass index, kg/m <sup>2</sup> (IQR)	26.1 (25.2–28.9)	27.4 (25.6–30.9)	0.242
Median Charlson comorbidity index (IQR)	4 (4–4)	3 (2.5–5)	0.625
Smokers, n (%)	6 (24)	7 (29)	0.754
Positive DRE, n (%)	18 (72)	16 (76)	0.999
Median PSA, ng/ml (IQR)	12.3 (7.7–24.3)	10 (7.5–13.5)	0.168
Median Gleason score (IQR)	7 (7–8)	7 (7–8)	0.289
Median number of total cores, n (IQR)	12 (12–12)	12 (12–14)	0.217
Median number of positive cores, n (IQR)	4 (3–8)	3 (2–4)	0.055
Median percentage positive cores, % (IQR)	25 (17–71)	21 (13–27)	0.272

DRE = digital rectal examination; IQR = interquartile range; PSA = prostate-specific antigen.

<sup>a</sup> Group A: intravesical sodium hyaluronate/sodium chondroitin sulfate plus oral chondroitin sulphate, hyaluronic acid, quercetin, and curcumin. Group B: no intravesical or oral treatment.

**Table 2 – Radiotherapy treatment parameters**

	Group A (n=25)	Group B (n=24)	p value
Median number of sessions (interquartile range)	36 (29–36)	36 (30–37)	0.470
Median dose, Gy (interquartile range)			
Prostate	72 (71–72)	72 (71–74)	0.432
Seminal vesicles	65 (56–65)	65 (65–67)	0.170
Lymph nodes	45 (45–49)	46 (45–48)	0.724
Bladder	44 (36–46)	44 (32–47)	0.941

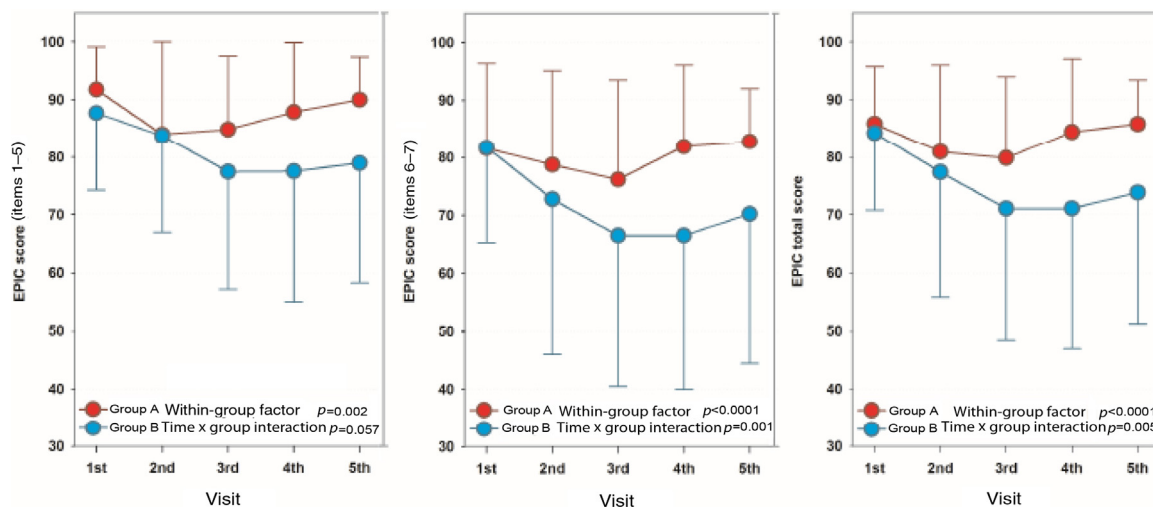
**Table 3 – Results for the urinary domain of the Expanded Prostate Cancer Index Composite<sup>a</sup>**

Item	Group A	WG p value	Group B	WG p value	BG p value	MD BG (95% CI)
<b>Visit 1 (baseline)</b>						
Number of patients	25		21			
1. Over the past 4 weeks, how often have you leaked urine?	84 ± 29.7		76.2 ± 34.9		0.426	
2. Over the past 4 weeks, how often have you urinated blood?	100 ± 0		100 ± 0		1.000	
3. Over the past 4 weeks, how often have you had pain or burning with urination?	96 ± 9.4		94 ± 17.5		0.930	
4. Which of the following best describes your urinary control during the last 4 weeks?	77.5 ± 20.9		79.5 ± 26.8		0.516	
5. How many pads or adult diapers per day did you usually use to control leakage during the last 4 weeks?	96 ± 14.7		88.9 ± 26.5		0.266	
Total for items 1–5	90.7 ± 10.5		87.7 ± 13.5		0.727	
6. How big a problem, if any, has each of the following been for you during the last 4 weeks?	79.7 ± 15.8		82.7 ± 16.4		0.431	
7. Overall, how big a problem has your urinary function been for you during the last 4 weeks?	77 ± 19		76.2 ± 20.1		0.981	
Total for items 6–7	79.3 ± 15.3		81.8 ± 16.6		0.492	
Total for items 1–7	84 ± 11		84.3 ± 13.5		0.604	
<b>Visit 5</b>						
Number of patients	23		21			
1. Over the past 4 weeks, how often have you leaked urine?	77.2 ± 30.1		64.3 ± 37.6		0.247	
2. Over the past 4 weeks, how often have you urinated blood?	98.9 ± 5.2		94 ± 13.5		0.124	
3. Over the past 4 weeks, how often have you had pain or burning with urination?	96.7 ± 8.6		86.9 ± 23.2		0.46	
4. Which of the following best describes your urinary control during the last 4 weeks?	78.4 ± 19		70 ± 20.9		0.178	
5. How many pads or adult diapers per day did you usually use to control leakage during the last 4 weeks?	98.6 ± 6.9		79.4 ± 34.1		0.012	
Total for items 1–5	90 ± 7.7		78.9 ± 20.7		0.096	
6. How big a problem, if any, has each of the following been for you during the last 4 weeks?	83.7 ± 9.3		71.4 ± 25.9		0.228	
7. Overall, how big a problem has your urinary function been for you during the last 4 weeks?	79.3 ± 16.3		63.1 ± 26.9		0.033	
Total for items 6–7	83.1 ± 9.1		70.2 ± 25.7		0.157	
Total for items 1–7	85.9 ± 7.7		73.9 ± 22.6		0.126	
<b>Change from baseline to visit 5</b>						
1. Over the past 4 weeks, how often have you leaked urine?	–9.8 ± 21	0.034	–11.9 ± 21.8	0.021	0.665	2.1 (–10.9 to 15.1)
2. Over the past 4 weeks, how often have you urinated blood?	–1.1 ± 5.2	0.317	–6 ± 13.5	0.059	0.124	4.9 (–1.2 to 11)
3. Over the past 4 weeks, how often have you had pain or burning with urination?	1.1 ± 9.2	0.564	–7.1 ± 26.4	0.230	0.144	8.2 (–3.6 to 20)
4. Which of the following best describes your urinary control during the last 4 weeks?	–1.4 ± 15.7	0.655	–9.5 ± 23.9	0.150	0.107	8.1 (–7.7 to 23.8)
5. How many pads or adult diapers per day did you usually use to control leakage during the last 4 weeks?	0 ± 0	1	–9.5 ± 23.9	0.084	0.070	9.5 (–0.5 to 19.6)
Total for items 1–5	–2.2 ± 6.4	0.776	–8.8 ± 18.5	0.050	0.209	6.6 (–1.7 to 14.8)
6. How big a problem, if any, has each of the following been for you during the last 4 weeks?	2.2 ± 10.9	0.138	–11.3 ± 15.8	0.005	0.002	13.5 (3.3–22.9)
7. Overall, how big a problem has your urinary function been for you during the last 4 weeks?	0 ± 13.1	1	–13.1 ± 18.7	0.009	0.016	13.1 (3.3–22.8)
Total for items 6–7	1.9 ± 10.5	0.819	–11.6 ± 15.5	0.003	0.003	13.5 (5.4–21.4))
Total for items 1–7	0.1 ± 7.1	0.592	–10.4 ± 16	0.008	0.006	10.5 (3.2–18)

BW = between groups; CI = confidence interval; MD = mean difference; WG = within-group.

<sup>a</sup> Score results are presented as mean ± standard deviation.





**Fig. 2 – Repeated-measures analysis of variance for the urinary domain of the Expanded Prostate Cancer Index Composite (EPIC). Data are presented as mean ± standard deviation.**

**Table 4 – Results for the International Consultation on Incontinence Questionnaire-Male Lower Urinary Tract Symptoms**

	Group A	WG p value	Group B	WG p value	BG p value	MD BG (95% CI)
<b>Visit 1 (baseline)</b>						
Number of patients	25		21			
Total score	15.6 ± 5.7		15.1 ± 7.6		0.921	
Voiding symptoms score	5.9 ± 4.3		6.6 ± 4.3		0.542	
Incontinence symptoms score	6.4 ± 3.0		5.5 ± 3.3		0.385	
Bother score	16.6 ± 13.9		16.1 ± 16.4		0.635	
<b>Visit 5</b>						
Number of patients	24		21			
Total score	17.9 ± 6.5		20.4 ± 8		0.202	
Voiding symptoms score	7.6 ± 4.7		7.4 ± 4.3		0.982	
Incontinence symptoms score	6.3 ± 3.4		9.3 ± 4.9		0.017	
Bother score	13.5 ± 9.5		27.4 ± 24.6		0.099	
<b>Change from visit 1 to visit 5</b>						
Total score	2.3 ± 3.8	0.019	5.2 ± 7.9	0.008	0.391	-2.9 (-6.7 to 0.7)
Voiding symptoms score	1.7 ± 3.1	0.007	0.8 ± 4.1	0.270	0.280	0.9 (-1.3 to 3)
Incontinence symptoms score	-0.1 ± 2.2	0.877	3.8 ± 5.0	0.004	0.004	-3.9 (-6.1 to -1.6)
Bother score	-1.6 ± 6.7	0.19	11.3 ± 15.4	<0.0001	<0.0001	-12.9 (-19.9 to -5.9)

BW = between groups; CI = confidence interval; MD = mean difference; WG = within-group.  
<sup>a</sup>Score results are presented as mean ± standard deviation.

symptoms score ( $p = 0.011$ ) and bother score ( $p = 0.017$ ), with higher scores in group B than in A (Fig. 3).

There were no significant differences between the groups in overall EQ-5D-5L scores at baseline. Group A had a significantly higher score for the Health today item at 12 mo when compared to group B ( $p = 0.028$ ). These data are summarised in Table 5.

RM-ANOVA revealed a statistically significant within-subjects factor over time ( $p = 0.039$ ) and a significant time × group interaction ( $p < 0.0001$ ), with a higher score in group A than in B for the Health today domain only (Fig. 4).

Intravesical treatment was very well tolerated, as substantiated by full compliance for all patients, who retained the intravesical solution in the bladder for at least 30 min without any distress. Overall, there were seven mild-to-moderate (grade 1–2) drug-related adverse events, including haematuria, nausea, and urticaria reported by

three patients. There were no serious (grade 3–4) drug-related adverse events or treatment-related withdrawals.

#### 4. Discussion

To the best of our knowledge, MISTIC is the first unblinded randomised controlled trial (active treatment vs no treatment in addition to RT) on the prevention of radiation-induced cystitis assessing a broad range of urinary symptoms and QoL using specific questionnaires.

Although new precision medicine RT modalities aim to personalise RT based on individual radiosensitivity, the number of patients affected by acute and late radiation cystitis is still relatively high and remains a challenge for health care systems [11]. Available options at present include different drugs for acute cystitis (anti-inflammatory, antibiotics, analgesics, antimuscarinics), bladder irrigation (with

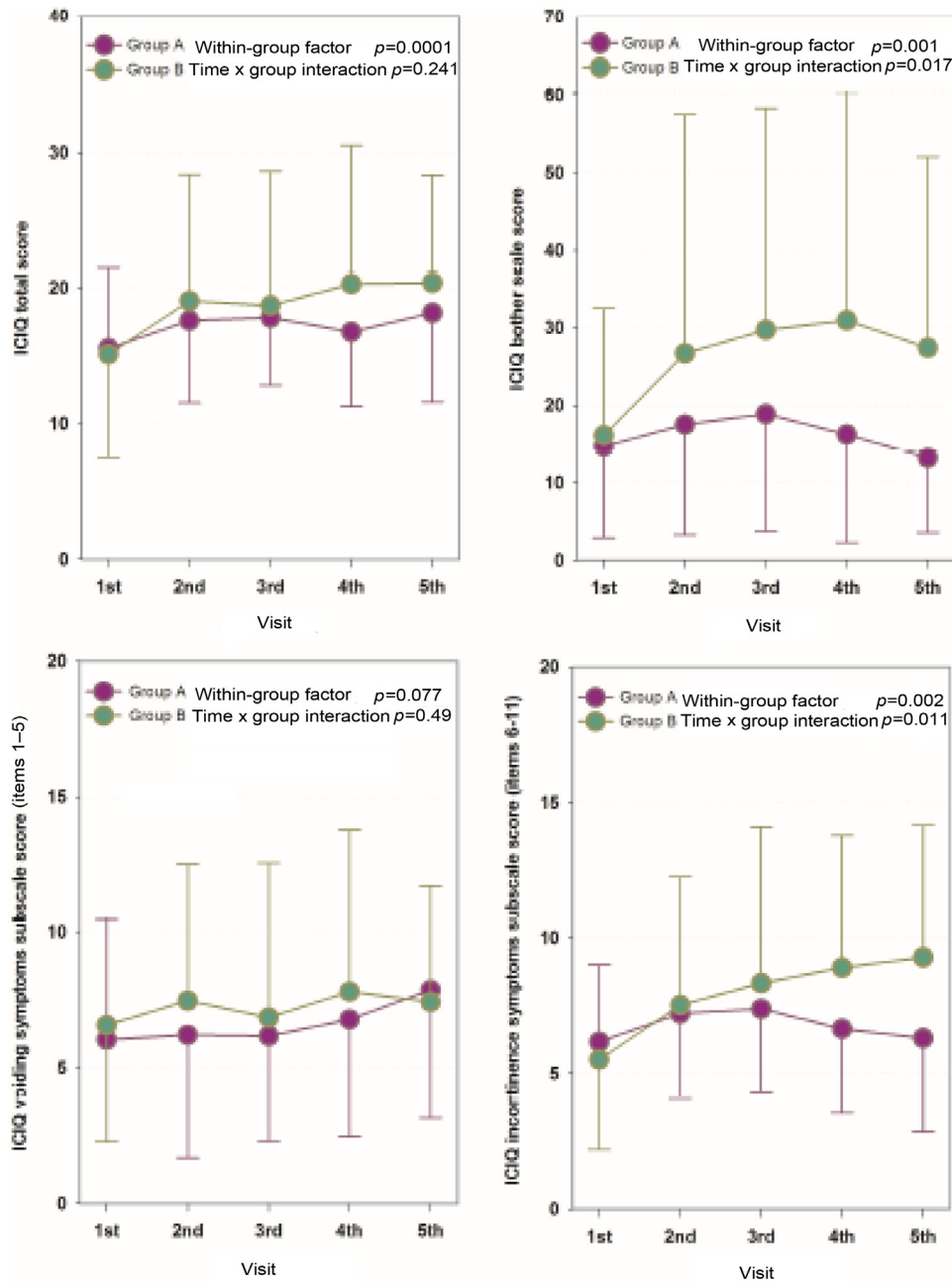


Fig. 3 – Repeated-measures analysis of variance for the International Consultation on Incontinence Questionnaire-(ICIQ) Male Lower Urinary Tract Symptoms. Data are presented as mean  $\pm$  standard deviation.

saline or specific solutions such as alum, silver nitrate, formalin, HA, and HA/CS), coagulation or selective embolisation of bleeding vessels, and hyperbaric oxygen therapy for chronic conditions [3,9]. These modalities are not always successful, and radical cystectomy is the only remaining option for severe chronic intractable radiation cystitis.

Only a few studies have tried to investigate a preventive strategy and timing of the intervention. Some have shown that a shorter time from RT to treatment may positively improve patient outcomes, supporting the need for early treatment to alleviate or prevent urinary symptoms [17]. In the current study, we started intravesical instillation and

oral treatment concurrently with RT initiation and continued the oral treatment for 12 wk. The aim was to protect the patient from acute radiation-induced bladder injuries and to prevent a negative outcome over time by consolidating the protection of the urothelium.

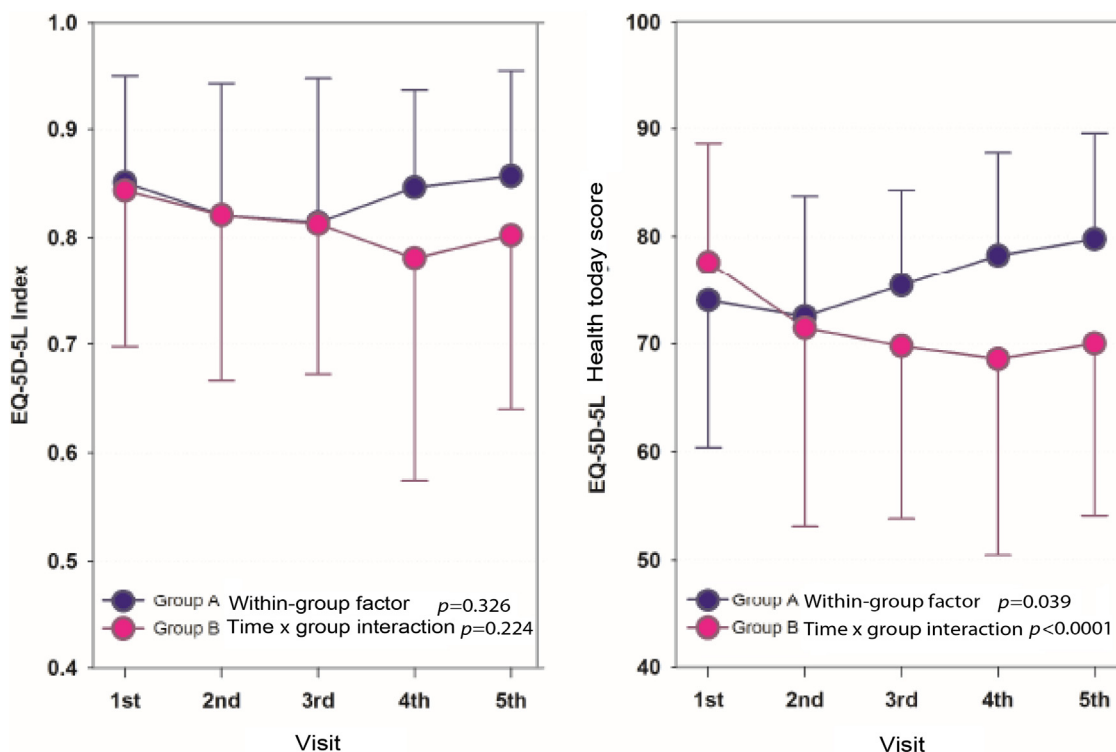
A limited number of single-centre, nonrandomised, and underpowered studies assessed the use of intravesical HA/SC for the treatment of radiation-induced cystitis, although this treatment has been extensively investigated for recurrent urinary tract infection and LUTS [18,19]. In a study of 23 consecutive patients with symptomatic cystitis after external RT for prostate cancer, Gacci et al [20]

**Table 5 – Results for the EuroQol Group EQ-5D-5L questionnaire<sup>a</sup>**

	Group A	WG <i>p</i> value	Group B	WG <i>p</i> value	BG <i>p</i> value	MD BG (95% CI)
Visit 1 (baseline)						
Number of patients	25		21			
Index score	0.858 ± 0.09		0.843 ± 0.15		0.578	
Health today score	74 ± 13.6		77.6 ± 11		0.510	
Visit 5						
Number of patients	24		21			
Index score	0.857 ± 0.1		0.802 ± 0.16		0.177	
Health today score	79.8 ± 9.8		70 ± 15.9		0.028	
Change from visit 1 to visit 5						
Index score	-0.001 ± 0.04	0.972	-0.041 ± 0.15	0.266	0.190	0.04 (-0.02 to 0.1)
Health today score	4.8 ± 8.1	0.05	-7.6 ± 13.1	0.021	0.002	12.4 (5.9–18.9)

BW = between groups; CI = confidence interval; MD = mean difference; WG = within-group.

<sup>a</sup> Score results are presented as mean ± standard deviation.



**Fig. 4 – Repeated-measures analysis of variance for the EuroQol Group EQ-5D-5L questionnaire. Data are presented as mean ± standard deviation.**

observed a significant impact on nocturnal voiding frequency on logistic regression analysis (Interstitial Cystitis Symptoms Index Q3:  $r=0.293$ ,  $p=0.011$  and  $r=0.970$ ,  $p<0.001$ ). In our series we considered urinary symptoms, not only nocturia, as well as QoL, using specific tools to investigate changes from baseline to 12 mo. The results for all questionnaires showed an improvement in QoL and symptoms in patients who received the active treatment (group A).

In the current study we combined intravesical HA/CS, a well-documented treatment for LUTS, with a similar oral preparation containing HA/CS and two dietary supplements. To the best of our knowledge, this is the first trial to combine the two formulations. There is a rationale in the

literature for the use of dietary supplements to treat radiation-induced urinary symptoms, but it is limited to a number of single-centre and underpowered studies. It is thought that dietary supplements can have an impact on mild to moderately severe acute radiation-induced cystitis. Products containing flavonoids, anthocyanins, and proanthocyanidins with strong antioxidant and anti-inflammatory characteristics may protect the urothelium from free radical damage. Campbell et al [21] investigated the effects of cranberry juice, which contains flavonoids, and other antioxidant and anti-inflammatory agents on acute radiation cystitis in patients with prostate cancer. Unfortunately, they did not find any statistically significant difference in cystitis severity between the group using



cranberry juice and the control juice group. On the contrary, Bonetta et al [22] reported a significant decrease in cystitis symptoms among 370 prostate cancer patients taking standardised cranberry capsules during RT for prostate carcinoma. However, the study was not randomised and the study design appeared to be poor. Hamilton and co-workers [23] carried out a double-blind placebo-controlled, under-powered pilot study in 41 prostate cancer patients who took cranberry capsules (containing 72 mg of proanthocyanidins) or placebo during RT treatment and for 2 wk after treatment completion. They observed a small but statistically significant decrease in the incidence of pain/burning and nocturia and an improvement in urinary flow strength [23]. These results were not confirmed in a recent large multicentre, double-blind, randomised, placebo-controlled clinical trial in which patients were instructed to take two cranberry capsules every day during RT and for 2 wk after treatment [24]. The severity of acute radiation cystitis was investigated using the modified Radiation Therapy Oncology Group grading system, the validated O'Leary Interstitial Cystitis Symptom and Problem Scale, and the novel Radiation-Induced Cystitis Assessment Scale. Contrary to expectations, the study failed to show that cranberry capsules were superior to placebo with respect to pain/burning, nocturia, and strength of urinary flow.

Curcumin, the main natural polyphenol found in the rhizome of *Curcuma longa*, has a benefit in inflammatory conditions because of its antioxidant effects [25]. Combination with quercetin, a flavonoid found in fruits and vegetables that has unique anti-inflammatory properties, improves the intestinal absorption and bioavailability of curcumin [26,27]. In addition, experimental evidence suggests that the combination has a role as a potential radioprotective factor [28]. Saadipoor et al [29] conducted a randomised, double-blind, placebo-controlled phase 2 trial of nanocurcumin in prostate cancer patients undergoing RT. Sixty-four patients with prostate cancer were randomised to receive oral nanocurcumin (120 mg/d) or placebo 3 d before and during the course of RT. No significant between-group difference in radiation-induced cystitis was observed. Fersino et al [30] performed a randomised controlled trial in 40 patients who were randomised (1:1) to receive RT alone or RT combined with iAluRil Soft Gels. The authors used the International Prostate Symptom Score (IPSS) questionnaire to investigate clinical outcomes. Although the IPSS is not designed to capture the specific study population, iAluRil Soft Gels appeared to have a beneficial role in reducing genitourinary toxicity. In our study, we used a combination of intravesical HA/CS and an oral preparation containing HA, CS, curcumin, and quercetin, and assessed outcomes using a specific questionnaire for the study cohort (ie, EPIC). The concordance between the three different questionnaires and the randomised study design support a high level of evidence from our findings.

The study has some limitations. The lack of a placebo and/or sham strategy group is the major drawback of the present RCT. Unfortunately, choice of the dose and duration for oral treatment was purely empirical. Although the intravesical schedule was modulated in

accordance with previous experience with intravesical HA/CS for the treatment of urinary tract infections or painful bladder syndrome, no evidence-based schedule exists for the dietary supplement. No data are reported on the use of medical treatment for LUTS (eg, anticholinergics, analgesics, hyperbaric oxygen) or the number of readmissions for lower urinary tract complications (eg, haematuria). Furthermore, many patients who undergo pelvic RT also have symptoms from adjacent organs, such as the rectum and genitalia. We did not investigate these scenarios in our series and we recognise the need for future studies to address these important aspects. The non-negligible rate of patients presenting with pre-existing LUTS related to benign prostate hyperplasia in our series might represent a confounding bias. However, this potential bias is balanced by the randomisation. Finally, our observations stopped after 1 yr and we have no long-term follow-up data.

## 5. Conclusions

In conclusion, our study shows a beneficial effect of intravesical HA-SC plus the oral combination of curcumin, quercetin, HA, and CS for prevention of acute and radiation-induced cystitis. Although the improvement in symptoms was maintained after 1 yr, our findings do not allow any conclusions regarding the intermediate- and long-term effects of oral and intravesical preparations on the risk of late radiation-induced cystitis.

**Author contributions:** Massimo Lazzeri had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Lazzeri.

*Acquisition of data:* Sanguedolce, Palou Redorta, Romancik, Lunik, Vittori, Di Maida, Colombo, Serretta, Çetinel.

*Analysis and interpretation of data:* Sanguedolce, Palou Redorta, Lazzeri.

*Drafting of the manuscript:* Lazzeri, Corradengo.

*Critical revision of the manuscript for important intellectual content:* Palou Redorta, Minervini.

*Statistical analysis:* Bini.

*Obtaining funding:* None.

*Administrative, technical, or material support:* None.

*Supervision:* Palou Redorta.

*Other:* None.

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