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Radiation Proctitis: The Potential Role of Hyaluronic Acid in the Prevention and Restoration of Any Damage to the Rectal Mucosa among Prostate Cancer Patients Submitted to Curative External Beam Radiotherapy

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Abstract: Aim: To evaluate if hyaluronic acid reduces proctitis episodes with respect to corticosteroids in prostate cancer patients submitted to radical or adjuvant radiotherapy. **Methods:** A consecutive series of eligible patients received hyaluronic acid enemas as supportive care (experimental group, from January 2013 to June 2015). A historical group (control group), treated from October 2011 to December 2012, received beclomethasone dipropionate suppositories. We registered each patient's data regarding acute and chronic proctitis. All patients were treated with static-intensity-modulated radiotherapy coupled to a daily set-up verification with orthogonal anterior–posterior/lateral X-ray pairs. **Results:** A total of 269 patients, 175 in the experimental group and 94 in the control group, was evaluated; 2 Gy/day (up to a total median dose of 80 Gy) and 2.7 Gy/day (up to a total median dose of 67.5 Gy) fractionation schemes were used for 216 and 53 patients, respectively. All patients had a good tolerance to radiotherapy, reporting no G3 or greater proctitis. No significant difference was reported concerning the total rate of proctitis between the two groups but only with respect to its grade: a higher G2 rate within the control group. There was no correlation between daily dose fractionation and toxicity grade. **Conclusions:** Hyaluronic acid enemas might be effective in reducing the severity of radiation proctitis.

Keywords: hyaluronic acid; beclomethasone dipropionate; radiation proctitis; prostate cancer; external beam radiotherapy; adverse events; supportive therapy

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1. Background/Aim

External beam radiotherapy (EBRT) represents a cornerstone in the treatment of localized prostate cancer. Some prospective comparative cohort studies have shown better tolerability for curative radiotherapy with respect to radical prostatectomy in terms of urinary toxicity and maintenance of sexual function [1,2]. Because of concerns about these side effects, non-metastatic prostate cancer patients do not infrequently prefer the first therapeutic option over the second one [3]. Furthermore, the advances in recent decades of external radiotherapy techniques (3D-conformal (3D-CRT) and intensity-modulated-(IMRT) and image-guided radiotherapy (IGRT)) have made it possible to minimize the incidence of adverse events (AEs) and to increase the radiation dose to the clinical target volume (CTV) [4–9]. Nonetheless, a certain rate of rectal toxicity remains among patients

undergoing radiotherapy for prostate cancer [10], especially if treated with regimens of hypofractionation of the radiation dose [11]. Indeed, moderate-severe radiation proctitis can affect a large proportion of prostate cancer patients, also in the standard fractionation scheme, if an escalated dose over 74 Gy is delivered [12]. Such a risk is almost halved by adopting IMRT and IGRT compared to 3D-CRT [13,14]. The image-guided radiation dose delivery-related gain in terms of proctitis risk reduction seems to be greater than that deriving from an accurate delineation of the radiotherapy target, e.g., by means of magnetic resonance imaging (MRI) [15], as in other clinical scenarios [16,17]. What further complicates the prediction of rectal toxicity is the inadequate reproducibility of the position of the rectum. In fact, this organ is subject to considerable interfraction variations based on rectal filling, the magnitude of which is able to give rise to an actual dosimetric distribution that could significantly differ from that planned in simulated CT scans [18]. In the light of the above, it is clear that the need for adequate topical therapy cannot be ignored to limit the onset of acute and chronic RT-related side effects in the rectum in subjects irradiated to the prostate for curative purposes. The mechanism of radiation-induced damage to the rectal mucosa derives from an inflammatory process, which, from an acute condition, may develop into a chronic one [19]. A chronic alteration of rectal function can have harmful implications on the quality of life of patients irradiated for prostate cancer [20,21].

As we are aware of the usefulness of hyaluronic acid to prevent and restore mucous membranes in other radiation-injured locations (vagina, skin and bladder) [22–25], we wanted to test the efficacy of such a medication in the prevention of acute and chronic proctitis among patients irradiated to the prostate or prostate bed. Here, we report the rectal toxicity data comparison for prostate cancer patients submitted to IMRT and, concomitantly, to the daily administration of hyaluronic acid enemas or topical corticosteroids.

2. Materials and Methods

For this study, we chose to compare two patient groups treated according to our institutional practice for prevention of rectal toxicities during curative radiotherapy for prostate cancer. From January 2013 to June 2015, eligible men who were localized prostate cancer candidates for adjuvant or radical radiation therapy were enrolled in the experimental group, which was treated with topical hyaluronic acid. This group was compared with eligible patients within the historical control group, who were treated in the same therapeutic setting from October 2011 to December 2012 with our previous standard supportive care, represented by topical corticosteroids. During the time periods, there were no radiotherapy treatment protocol changes in our institution. The patients enrolled in the experimental group were invited to daily self-administer hyaluronic acid enriched with a pool of amino acid excipients (glycine, L-proline, L-leucine, L-lysine hydrochloride) in a 7 gr enema using an applicator at night before sleeping, starting from the first day of radiotherapy, for its entire duration and up to two weeks after the end of radiotherapy. The historical group was composed of patients treated with rectal beclomethasone dipropionate suppositories, administered with the same dosing regimen as the hyaluronic group. In both groups, according to our daily practice, a radiation oncologist and a nurse made clinical assessments (including the anal area) at the start of irradiation; weekly, during treatment; at the end of radiotherapy; and during follow-up. Nurses instructed the patients on how to perform the enema and interviewed them weekly to ensure that the medication was used daily.

The eligibility criteria were: signed informed patient consent, total prescribed dose $\geq$ 60 Gy, no inflammatory bowel disease, no concomitant use of oral or parenteral corticosteroids, no previous pelvic radiotherapy, and no rectal issues (e.g., hemorrhoids, fissures, fistula, cancer). The proposed radiotherapy treatment consisted of a normo- or, in the case of radical radiotherapy, moderately hypofractionated (2.7 Gy dose/fraction) schedule and was delivered with 6-MV energy photons and with static IMRT (seven-fields technique), after computed tomography (CT) simulation with 3 mm thickness slices in the supine position with a dedicated immobilization device. All patients were required to fill

their bladder before the simulation and every-day treatment in order to push away the intestinal loops from the radiotherapy target by drinking 500 ccs of water 30 min before set-up positioning. The CTV (prostate ± seminal vesicles or prostate bed) was given an asymmetrical safety margin of 10 mm in the cranio-caudal, latero-lateral, and anterior directions, while a 5 mm margin was applied posteriorly, thus identifying the planning target volume (PTV). For the contouring of the organs at risk, we relied on the Radiation Therapy Oncology Group (RTOG) atlas. Set-up verification was conducted daily with orthogonal anterior–posterior/lateral X-ray pairs (MV-MV). The prescription of the radiation dose was performed according to the International Commission on Radiation Units and Measurements (ICRU) recommendations and with due regard for the dose-volume constraints suggested by Quantitative Analyses of Normal Tissues Effects in the Clinic (QUANTEC). As a guarantee of an acceptable theoretical rate of radio-induced toxicity, we pursued a dose to the rectum consistent with the following constraints: V65 Gy < 17% and V40 Gy < 35% for conventionally fractionated radiotherapy; V46 < 30% and V37 < 50% for a hypofractionated schedule. We also tried to minimize the portion of anterior rectal wall exposed to a high radiation dose through both plan optimization and dietary suggestions. At the time of the CT simulation, all patients were recommended to keep regular bowel function as much as possible in order to have an empty rectum and, therefore, decrease the amount of anterior rectal wall covered by the 90% isodose line. All these solutions, especially the dosimetric goals, were strictly required to collect comparable patients' reports regarding the baseline rectal issue. Acute rectal toxicity was assessed according to the RTOG criteria and chronic rectal toxicity according to the RTOG/European Organisation for Research and Treatment of Cancer (EORTC) criteria, recorded weekly during radiotherapy and monthly after the end.

3. Statistical Analysis

The endpoint of the study was the evaluation of acute and chronic toxicity rates in the two patient groups. Associations between variables were analyzed; a chi-squared test was used for estimating group differences between the experimental arm and the control arm. Correlations between age and radiation proctitis frequency and severity were investigated by a one-way ANOVA test. Statistical analysis was performed using MedCalc for Windows, version 19.4 (MedCalc Software, Ostend, Belgium); $p < 0.05$ was considered statistically significant.

4. Results

During the study period (from October 2011 to June 2015), we observed 297 prostate cancer patients suitable for curative irradiation. Among these, there were 94 patients eligible to form the control group; 175 patients formed the experimental group (Figure 1). All registered patients' rectal toxicity data were collected retrospectively. The median age of the entire sample was 75 years (range 52–92). Two hundred and sixteen patients were treated with a normofractionated schedule (2 Gy/day) and 53 with a hypofractionated schedule (2.7 Gy/day). The median dose of the normofractionated group was 80 Gy (range 54–80 Gy) and that of the hypofractionated group was 67.5 Gy (range 62.1–70 Gy). Patients' characteristics are summarized in Table 1.

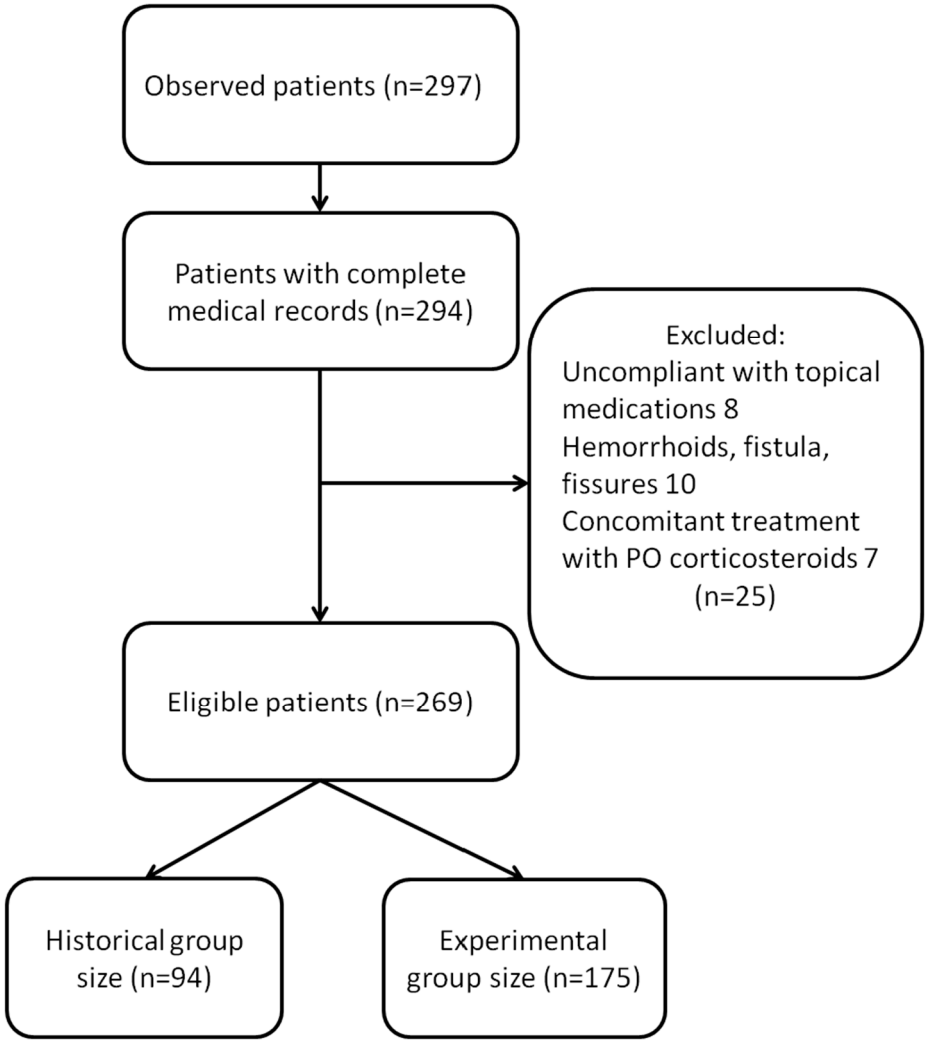

Figure 1. Flowchart of the patient enrollment process of the study cohort.

Table 1. Patients' characteristics.

	Conventional Fractionation (54–80 Gy)	**Hypofractionation (62.1–70 Gy)**	**Total**
No of patients	216 (80.3%)	53(19.7%)	269
Age			
Range	52–85	60–92	52–92
Median	73	82	75
Radiotherapy			
Radical	104(48.15%)	51(96.2%)	155(57.6%)
Adjuvant	112(51.85%)	2(3.8%)	114(42.4%)
Medications			
Hyaluronic acid	129(59.7%)	46(86.8%)	175(65%)
Beclomethasone dipropionate	87(40.3%)	7(13.2%)	94(35%)

The follow-up period was 3 months for monitoring acute toxicity, while chronic toxicity was evaluated for at least 60 months after the end of radiation therapy. All patients completed the enema treatment. No patient developed rectal toxicity greater than or equal to G3. The absolute numbers of the acute and late rectal toxicities, divided by grade in both medication groups, are reported in Table 2.

Table 2. Summary of rectal toxicities.

Hyaluronic Acid Group			
Proctitis grade	G0	G1	G2
Acute	77(44%)	90(51.4%)	8(4.6%)
Late	150 (85.7%)	22(12.6%)	3(1.7%)
Beclomethasone Dipropionate Group			
Proctitis grade	G0	G1	G2
Acute	32(34.1%)	51(54.2%)	11(11.7%)
Late	72(76.6%)	15(16%)	7(7.4%)

By dividing each group (that of hyaluronic acid and that of beclomethasone dipropionate) into two subgroups (no toxicity (G0) vs. toxicity (>G0)), we did not find any significant difference in occurrence between the control and experimental groups for both acute and chronic toxicity ($p > 0.05$), as shown in Table 3.

Table 3. Comparison between hyaluronic acid and beclomethasone dipropionate groups on the basis of symptomatic acute and late proctitis (≥G1) rate, considering both hypofractionation and standard fractionation of the radiation dose. Legend: No Tox is for the no-toxicities group (=G0), Tox is for the toxicities group (≥G1).

Overall Acute Toxicity					
GRADE	**Hyaluronic Acid**	**Beclomethasone Dipropionate**		**Chi-Squared Test**	
No Tox	77(44%)	32(34%)	109(40.5%)	Chi-squared	2.12
				DF	1
Tox	98(56%)	62(66%)	160(59.5%)	Significance level	$p = 0.1454$
	175(65.1%)	94(34.9%)	269		
Overall Late Toxicity					
GRADE	**Hyaluronic Acid**	**Beclomethasone Dipropionate**		**Chi-Squared Test**	
No Tox	150 (85.7%)	72 (76.6%)	222 (82.5%)	Chi-squared	2.922
				DF	1
Tox	25 (14.3%)	22 (23.4%)	47 (17.5%)	Significance level	$p = 0.0874$
	175 (65.1%)	94 (34.9%)	269		

Similarly, the rate of acute and chronic G1 toxicity did not differ significantly between the two groups ($p > 0.05$). Conversely, the rate of acute G2 toxicity was significantly lower in the hyaluronic acid group ($p < 0.05$) as well as that of chronic G2 toxicity ($p < 0.05$) (Table 4). Between the historical and the experimental groups, the odds ratio (OR) was equal to 0.36 for acute G2 toxicity and 0.16 for chronic G2 toxicity in favor of hyaluronic acid over beclomethasone dipropionate.

Table 4. Acute G1 and G2 and late G1 and G2 rectal toxicities rates among hyaluronic acid and beclomethasone dipropionate groups.

GRADE		**Hyaluronic Acid**	**Beclomethasone Dipropionate**	***p*-Value**
G1	Acute	51.4%	54.3%	0.750
	Late	12.6%	16.0%	0.560
G2	Acute	4.6%	11.7%	0.046
	Late	1.7%	7.4%	0.042

There was no correlation between daily dose fractionation and toxicity grade in the entire cohort as well as in either of the two medication groups ($p > 0.05$). Not even radiotherapy target (prostate vs. prostate bed) influenced the proctitis risk, both overall

and in any subgroup ($p > 0.05$). We identified no age threshold or group at higher risk of proctitis.

No patient needed to deviate from the prescribed supportive therapy, and no enema-related complications were observed: compliance was good for all patients, with no additional topical or systemic treatment required except for one patient in the normofractionated group who voluntarily stopped the radiation treatment three daily fractions before the end of the planned schedule due to G2 genitourinary toxicity.

5. Discussion

Our study is one of the few to investigate the potential role of hyaluronic acid in proctitis prevention. The systematic use of this molecule from the start of the radiotherapy course does not appear to negatively affect the tolerance of the rectum to the high radiation doses, commonly used for curative intent among localized prostate cancer patients. Indeed, the rate of symptomatic patients (>G0) did not differ significantly between the two medication groups. Of particular note is the fact that no patients developed grade $\geq$3 proctitis in the acute phase or the chronic phase; additionally, none of them interrupted their radiotherapy program due to a compliance-threatening rectal discomfort. This finding might promote the systematic use of a mucosal restorative or anti-inflammatory topical therapy from the first to the last day of radiotherapy treatment. Actually, in the face of a large number of patients that developed certain rectal toxicity (at least grade G1), only a small minority complained of episodes of proctitis of clinical relevance ($\geq$G2) that, on some occasions, required active treatment. The non-inferiority here of hyaluronic acid with respect to another widely used class of drug, namely, corticosteroids, is particularly significant, given that, in any case, these latter medications have a non-negligible toxicity profile, which thereby limits their prescription in certain circumstances (e.g., fissures, tenesmus, superinfections). Furthermore, the results reported by us show that hyaluronic acid could limit proctitis severity (a significantly higher rate of G2 toxicity in the corticosteroid group). The ORs suggest a significant rectal protection role for hyaluronic acid. Conversely, neither fractionation scheme (normofractionated vs. hypofractionated radiation dose) nor therapeutic setting (radical vs. adjuvant) correlated with rectal toxicity. Additionally, the lack of any correlation between proctitis risk and age also confirms the safety of radiotherapy treatment for genitourinary cancers among elderly populations [26].

To date, to our knowledge, this is the only other study to test the effectiveness of hyaluronic acid for topical endorectal administration in the prevention of proctitis associated with radiotherapy to the prostate. In fact, prior to our experience, Stefanelli et al. did not report a statistically significant difference in the incidence of acute rectal side effects between the group treated with a daily suppository of hyaluronic acid during prostate-directed radiotherapy and the historical control group with no daily supportive care but only a longer latency in the onset of proctitis [27]. However, this data should be stressed because it could imply an easier completion of the planned radiotherapy for the patient, as demonstrated for neoadjuvant radiotherapy for rectal cancer by Montrone et al. [28]. In fact, the application of hyaluronic acid in patients irradiated for prostate cancer is mostly transperineal (thus exploiting its function of an inert spacer between the radiotherapy target and the anterior rectal wall rather than that of a molecule for the active repair of radio-induced damage) and, with this route of administration, has shown particularly encouraging results [29–34], making even re-irradiation, if necessary, less risky [35,36]. Hyaluronic acid could be an alternative to local anti-inflammatory agents such as topical sulfasalazine, mesalazine, and corticosteroids, which reduce the synthesis of proinflammatory cytokines and mediators [37]. Some of the radiation-induced damage is mediated by the formation of reactive oxygen species (ROS) due to the interaction of ionizing radiations with water molecules. The removal and neutralization of the free radicals produced would explain the effectiveness of amifostine in the prevention of proctitis [38]. Similar antioxidant activity, albeit with a different mechanism, is postulated for hyaluronic acid [39]. This molecule has, among other things, proven effective in wound repair and

tissue regeneration [40]. Indeed, topical hyaluronic acid has already proven to be successful in preserving the function of other pelvic organs; in fact, this natural constituent of the extracellular matrix can boast evidence of efficacy deriving from randomized controlled trials in the prevention and treatment of vulvo-vaginitis among women undergoing pelvic radiotherapy [41] and in reducing nocturnal-voiding frequency among prostate cancer men with post-radiation bladder pain [42,43]. In addition, the intraperitoneal administration of hyaluronic acid before radiation has been shown to reduce radio-induced apoptosis and increase crypt survival in intestinal mucosa in mouse models [44]. It could be argued that the daily administration of topical corticosteroids may correspond to overtreatment that could lead to an underestimation of the effectiveness of hyaluronic acid. The daily use of corticosteroids is not actually supported by the most recent international guidelines [45], but our clinical practice was motivated by the evidence produced by Fuccio et al. [46], who, in a randomized clinical trial among irradiated prostate cancer patients, demonstrated a lower risk of rectal bleeding and better quality of life for patients daily treated with beclomethasone dipropionate compared to the those treated with placebo. In order to have a precise estimate of the therapeutic benefit of hyaluronic acid, we would have had to set up a control group with placebo, a circumstance which, given the high frequency of the symptom intended to be prevented, we considered ethically unfeasible. Furthermore, it is not possible to estimate the amount of proctitis induced by the unpredictable involvement of the rectal wall in the radiation field since the set-up verifications were conducted with orthogonal anterior–posterior/lateral X-ray pairs (MV-MV), the poor quality of which did not allow us to evaluate the rectal filling and position but only the matching with bony landmarks. For this reason, it would be advisable to conduct the same comparison when able to take advantage of a 3D-IGRT, which would allow us to define the weight of technological and clinical research [47] advancement on the one hand and of pharmaceutical products on the other, in determining the reduction of rectal toxicity that has been witnessed in the last few years.

The possible benefit of hyaluronic acid must, however, be re-discussed in the light of recent evidence that suggests a procancerous potential [48]. It would be worthwhile assessing what proportion of the exogenous hyaluronic acid film on the rectal mucosa is absorbed by the contiguous prostate and its effect on the microenvironment of cancer cells [49–51]. Finally, it is noteworthy to underline that hyaluronic acid enemas, being effective in reducing the severity of radiation proctitis, could also prevent anemia, which is not infrequently a consequence of proctitis, as recently reported [52].

6. Limitations

We are fully aware that such a work has several limitations, primarily due to its retrospective nature: the non-random nature of the assignment of patients to the two treatments presupposes a non-contemporaneous control bias that could weaken the results of the study [53]; the mere-symptoms assessment, according to the somewhat subjective RTOG/EORTC scales, was not supported by clinical–instrumental tests such as rectoscopy for objectively grading proctitis and could be affected by a Hawthorne effect [54]; the lack of a control group treated with placebo; inability to predict the in vivo dose accidentally delivered to the anterior rectal wall; numerical imbalance between the groups; heterogeneity in dose fractionation and radiotherapy timing (radical vs. adjuvant).

7. Conclusions

IMRT treatment for prostate cancer is generally well tolerated. Hyaluronic acid rectal enemas, administered daily, might have a role in the prevention of proctitis in patients undergoing curative static IMRT to the prostate or prostate bed, not having proved inferior to the daily beclomethasone dipropionate suppositories regarding rectal toxicity rates but being able to reduce its severity. Further studies are needed to confirm this hypothesis and clarify the usefulness of this pharmaceutical supplement even among prostate cancer patients treated with image-guided IMRT.

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Data Availability Statement: The data that support the findings of this study are available on request from the authors.

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