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Double-blind, randomized clinical study comparing hyaluronic acid cream to placebo in patients treated with radiotherapy

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Abstract

Purpose: The effect of hyaluronic acid (Ialugen® cream) on acute skin reactions after radiotherapy, was assessed in a randomized, double-blind, placebo-controlled study.

Material and methods: Out of the 152 patients presenting with head and neck, breast or pelvic carcinomas and registered in the study, 134 cases – 70 in the Ialugen group (IA) and 64 in the placebo group (PBO) – completed their IA or PBO treatment. At the time of randomisation, these two groups were balanced for sex, age, weight and height. The mean total dose of radiation given during the study was 60.6 ± 10.9 Gy in the IA group and 64.3 ± 10.8 Gy in the PBO group ($P = 0.47$).

Results: Acute radio-epithelitis scores were significantly higher in the PBO group than in the IA group, starting from the control at week 3 and throughout the 6 weeks of treatment ($P < 0.01$ from week 3 to week 7; $P < 0.05$ at weeks 8 and 10). Likewise, the global efficacy judgement expressed, at the end of treatment, by both the physician and the patient showed a significant difference in favour of Ialugen ($P < 0.01$ and $P < 0.05$, respectively). There was no significant difference of tolerance between the IA and PBO treatments ($P = 0.18$ according to the physician and $P = 0.42$ from the patient's viewpoint).

Conclusion: The prophylactic use of a cream with hyaluronic acid is shown to reduce the incidence of high grade radio-epithelitis, suggesting an interesting role of the hyaluronic acid cream as supportive treatment to improve compliance and quality of life in patients undergoing radiation therapy. © 1997 Elsevier Science Ireland Ltd.

Keywords: Radiotherapy; Head and Neck; Breast; Acute toxicity; Hyaluronic acid

1. Introduction

One of the dose-limiting effects of radiotherapy is the acute reaction that ionizing radiation induces in normal tissues. The severity of this acute toxicity is linked to some host-related factors such as age, diabetes or hypertension and to various treatment-related parameters such as total irradiation dose, dose per fraction and overall treatment time. The onset and the duration of both mucosal and skin reactions have also been shown to be influenced by an acceleration of the treatment [7], by the application of large fields of irradiation, or in the framework of treatments combining synchronously radio- and chemotherapy [1].

Skin toxicity is one of the major problems in patients irradiated for head and neck, breast and low pelvis carcinomas. The onset of acute radio-epidermitis can be observed in the early phase of the treatment and besides being a hindrance in the patient's quality of life, severe skin reactions significantly reduce the patient compliance to treatment, thereby reducing its efficacy. This is well documented for head and neck tumors, which recur significantly more often when treatment has to be delivered in more than 50 to 55 days [2].

Hyaluronic acid is one of the natural polymers belonging to the sulphated glycosaminoglycans class and represents the main component of the dermis extracellular matrix, where, besides having important mechanical and structural functions, it also plays a key role in the healing process. Briefly, hyaluronic acid stimulates the fibrin development, the neutrophilous granulocytes and macro-

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phages phagocytic mobility and activity, and further stimulates the release of chemotactic factors for the fibroblasts. Moreover, it induces the fibroblasts proliferation and stimulates their metabolism during the granulation phase of the healing process; with a subsequent increase in collagenous fibers and in fundamental substance deposition [3,6,9-11].

The present study analyses whether the prophylactic use of a cream with hyaluronic acid postpones the first signs of acute radio-epithelitis and/or reduces its severity. The study was also aimed at evaluating the already known reparatory efficacy of hyaluronic acid to delay the onset of necrosis or accelerate the recovery in case of ulceration [3,6,9,15].

2. Material and methods

This randomized, double-blind, placebo-controlled study was conducted over a 20-month accrual period. In each of the two institutions participating to the study, the patients were followed by only one physician.

2.1. Inclusion criteria

Patients of both sexes, ranging from 20 to 85 years, presenting with either a head and neck, pelvic or breast carcinoma of any stage, and given a fractionated radiation therapy were entered into the study.

2.2. Exclusion criteria

Excluded from the study were the patients with previous cutaneous diseases and those suffering from systemic diseases known to delay the skin healing process such as diabetes mellitus or severe renal failure.

2.3. Patient population

Out of the 152 patients registered in the study, 134 presenting with head and neck (90), breast (30) or pelvic carcinomas (14) were found to be eligible and randomly assigned to one of two treatment arms (placebo versus hyaluronic acid) using a computer-generated randomization list.

2.4. Radiotherapy treatment

In patients with head and neck tumors, radiation therapy was delivered through two parallel opposed portals. The total doses ranged from 66 Gy to 80.5 Gy. Patients receiving conventional fractionation (66 Gy) were given one daily session of 1.8 to 2 Gy. Patients treated according a hyperfractionated schedule (80.5 Gy) were given two daily sessions of 1.15 Gy each, with a minimum 6-h interval. Treatment techniques were based on photon beams of less

than 6 MeV and, in all patients, used electrons of less than 10 MeV for spinal chain lymph node irradiation.

Patients with breast carcinomas were treated according to a conventional fractionation of 2 Gy per day, up to a total dose of 60 to 66 Gy, through tangential portals. Photon beams of less than 10 MeV and electron beams of less than 15 MeV were used to treat this patient population.

Patients with pelvic carcinoma were also treated according to a conventional fractionation schedule of one daily session of 2 Gy, up to a total dose ranging between 60 and 66 Gy, delivered through a four-field ('box') technique. This latter group of patients was irradiated with a 15 MeV photon beam.

2.5. Hyaluronic acid compound

Hyaluronic acid 0.2% cream (Ialugen®) and placebo creams were provided by the Institut Biochimique S.A. (IBSA), Lugano, Switzerland. The two formulations were identical in appearance and could not be distinguished from each other. The base of the placebo and hyaluronic acid creams was the same and consisted of polyethylenglycol 400 monostearate, lipidic phase, glycerol, 70% sorbitol solution, preservatives, fragrance and purified water.

2.6. Hyaluronic acid cream application

Using the flat part of a tongue-depressor, sufficient amount of hyaluronic acid cream or placebo cream (0.4 mg/cm²) was applied to the irradiated skin area twice a day: the first application 1-2 h after the morning radiotherapy session, the second in the evening. The topical treatment of the irradiated area was continued over a 6-week period whereas the post-radiotherapeutic follow-up lasted 4 weeks. Patients were instructed to make self-application of the cream during the weekends. When the patients did not receive any radiotherapeutic treatment, the formulations were applied every day in the morning and in the evening. No concomitant medication was allowed over the whole period of treatment and observation.

2.7. Evaluation parameters

The patients were examined by the physician at the time of admission (Day 0) and once-a-week, by the same physician, over a 10-week period. The status of the irradiated skin surface was evaluated according to the following scale: 0, normal skin; 1, light epidermal irritation (consisting of the onset of skin redness, possibly associated to slight tenderness); 2, erythema with dry desquamation; 3, exudate <50%; 4, exudate >50%; 5, ulcer.

In case of ulcer, the healing process was reported as follows: 1, minimum and maximum lesion diameters (mm); 2, lesion cleansing; 3, beginning of the proliferation

process and proliferation of the tissue granulation; 4, re-epithelialisation.

At the end of the study, the physician gave a global judgement on the therapeutic efficacy and the tolerability of the two treatments by means of the following verbal scale: 0, poor; 1, fair; 2, good; 3, excellent.

Any side-effect observed during the study was reported on the patient 'Case Report Form'.

2.8. Statistical analysis

At the end of the study, all data obtained were submitted to a statistical and biometrics analysis which was carried out by an independent statistician. The raw data were processed using BMDP Statistical Software [5]. Population variables, homogeneity at the time of entry, patients and investigator assessments were analysed with either Student's *t*-test or Pearson chi-square test with the Yates correction. Sequential scores were compared according to the Wilcoxon test (intra-group variation) [4]. The variable 'status of the irradiated skin', scored according to the scale mentioned above, was analysed according to the following cut-off: Group 1, scores 0-1; Group 2, scores >1.

2.9. Ethical aspects

This study was conducted in accordance with the Principles of the Helsinki Declaration and the subsequent Tokyo and Venice amendments.

3. Results

3.1. Sample size and patient characteristics

A total of 152 patients were admitted into the study: 76 patients in the PBO group and 76 in the IA group. In 18 patients (6 treated with IA, 12 with PBO), the skin reaction assessment was found to have been limited to the first 4 weeks of treatment. Table 1 lists the causes of these protocol violations. These 18 cases were excluded from the analysis, leaving a total of 134 cases (70 treated with Ialugen and 64 with placebo).

These two groups were balanced for sex, age, weight

Table 1

Sample size and causes of exclusion

Causes of exclusion	Ialugen (IA)	Placebo (PBO)
Registered	76	76
Not assessed beyond the 4th week	3	4
Severe skin infection	1	33
Severe skin reaction	0	1
Poor compliance	2	3
Died during treatment	0	1
Analysed	70	64

Table 2

Patient characteristics

Characteristics	Ialugen	Placebo	P value
Sex (M/F)	34/36	40/24	0.09 ^a
Age (mean ± SD)	59.9 ± 12.7	55.7 ± 11.8	0.26 ^a
(min-max)	(33-89)	(24-82)	
Weight (kg ± SD)	65.5 ± 11.6	65.2 ± 13.5	0.11 ^a
(min-max)	(40-97)	(43-100)	
Height (cm ± SD)	166.1 ± 7.2	168.5 ± 7.2	0.46 ^a
(min-max)	(155-182)	(151-180)	
General conditions (%)			0.78 ^b
Good	38 (76)	36 (77)	
Fair	11 (22)	9 (19)	
Poor	1 (3)	2 (4)	
Type of tumor (%)			0.15 ^b
Head and neck	42 (60)	48 (75)	
Breast	20 (29)	10 (16)	
Pelvic	8 (11)	6 (9)	
Stage of disease (%)			0.97 ^b
Early	20 (41)	19 (40)	
Advanced	29 (59)	28 (60)	

^aStudent's *t*-test.

^bPearson chi-square test.

and height. In the head and neck cancer population, both irradiation schedules (1 versus 2 daily sessions) were equally distributed in the two treatment arms. The type of tumour and the stage of the disease were registered at study entry, as well as the general health conditions of the patient (Table 2). The mean total dose of radiation given during the study was 60.6 ± 10.9 Gy in the IA group and 64.3 ± 10.8 Gy in the PBO group (*P* = 0.47).

Among these 134 cases whose skin reaction was assessable during the first 5 weeks, patients who stopped thereafter their IA or PBO treatment because they had experienced a complete healing of their skin lesions during the irradiation period (3 in the IA arm; 3 in the PBO) or those who did not complete their 10-week follow-up (5 in the IA arm, 2 in the PBO) remained in the statistical analysis as long as their skin reaction status was assessed.

It is worth noting that the severe skin infections observed during or after radiotherapy were not linked to IA or PBO treatment but to the disease (one sub-mental abscess treated with drainage and antibiotics) or to mycosis in the infra-mammary sulcus or inguinal areas (*n* = 3).

3.2. Comparative analysis of acute skin reactions to radiotherapy

At the time of entry of patients into the study, there was no difference of skin status between the IA and the PBO groups (Fig. 1). The statistical analysis (Wilcoxon test) registered at the different times of observation showed a significant upgrading of the irradiated skin scores in the placebo group already after 1 week of radiotherapy (*P* < 0.01), lasting until the end of the study period. In the Ialugen group, a statistically significant difference was observed between baseline and sequential scores, after a

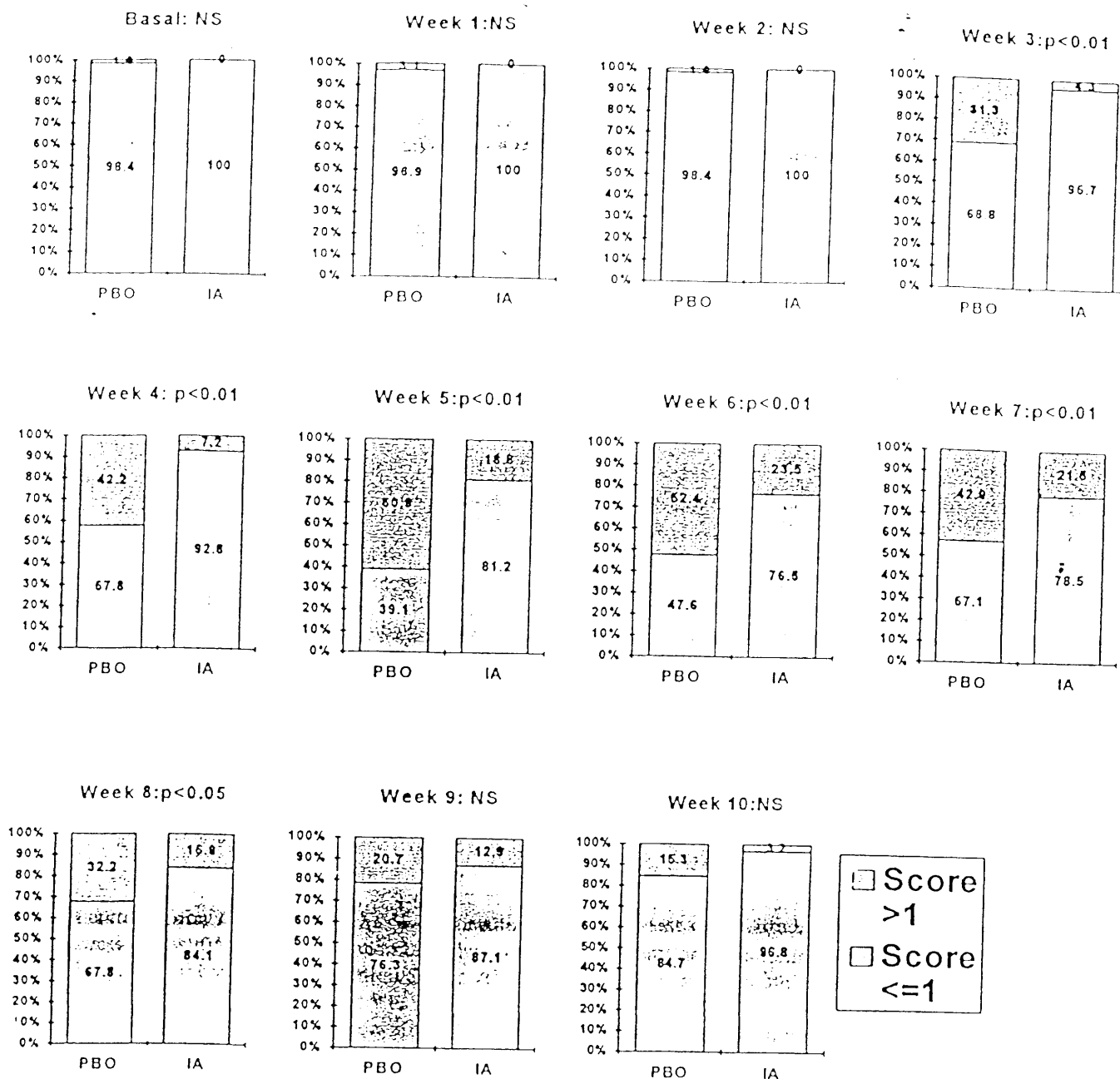


Fig. 1. Sequential analysis of irradiated skin status in 134 patients.

2-week observation period ($P < 0.01$) and lasting, as in the placebo group, until week 10.

The statistical comparison (Pearson chi-square test with Yates correction) of the skin reactions scores (0-1 versus 2-5) between the two treatments pointed out that there was a statistically significant difference in favour of the IA group starting from the control at week 3 and throughout the radiotherapy treatment ($P < 0.01$ from week 3 until week 7). A significant difference between the two treatments was still present at the first two controls of the follow-up period ($P < 0.01$ at week 7 and $P < 0.05$ at week 8). While no significant difference was observed at

week 9, the difference level was significant again at week 10 ($P < 0.05$).

Table 3 reports the distribution of relative incidences for each skin reaction score, over the 10-week observation period. Significant differences in reaction severity between the IA and the PBO groups were found from week 3 until week 7.

In the group of head and neck cancers ($n = 90$), the statistical comparison between the two treatments showed that there was also a significant difference in favour of the IA group for the following observation times: week 3, $P = 0.0003$; week 4, $P = 0.0001$; week 5, $P = 0.0035$.

Table 3
Distribution of skin reaction scores over the 10-week monitoring period*

Treatment group	Score	Basal	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
Ialugen	0	95.7	87	68.1	47.1	34.3	26.1	28.4	34.7	47.7	56.4	74.4
	1	4.3	13	31.9	48.5	58.2	55.1	47.8	42.9	34.1	28.2	20.5
	2				4.4	4.5	15.9	20.9	16.3	18.2	15.4	5.1
	3					3	2.9	3	4.1			
	4											
Placebo	0	95.3	75	53.1	28.1	9.5	4.7	3.2	9.3	31.8	36.8	68.4
	1	3.1	21.9	40.6	40.6	47.6	34.4	45.2	46.3	34.1	42.1	18.4
	2	1.6	1.6	3.1	26.6	31.7	43.7	32.3	29.6	22.7	13.2	5.3
	3		1.6	1.6	4.7	11.1	9.4	16.1	9.3	6.8	2.6	2.6
	4			1.6			6.2	1.9	1.9	2.6	2.6	2.6
	5					1.6	3.2	3.7	4.5	2.6	2.6	2.6
Pearson chi-square	P value	0.5447	0.2369	0.1819	0.0006	<0.0001	<0.0001	0.0002	0.0353	0.1573	0.3280	0.6684

*Results expressed in %.

3.3. Subgroup analysis: severe acute radio-epithelitis

In the PBO group, six acute reactions scored 4 while two patients presented a skin ulceration, scored 5. The average healing time for these severe acute radio-epithelitis was 2.25 weeks, with healing times ranging from 1 to 4 weeks. In the IA group, only one patient presented a severe skin reaction which nevertheless healed within 1 week.

Concerning the hyaluronic acid activity on the healing process of cutaneous lesions, the very small number of observations reported from the investigators for the parameters 'minimum and maximum lesion diameters', 'lesion cleansing', 'beginning of the proliferation process' and 'reepithelialisation', did not allow any statistical evaluation to be carried out.

3.4. Global efficacy evaluation

A global judgement on the therapeutic efficacy of the two treatments was expressed by the physician and by the patient (Table 4). In both cases, a statistically significant difference in favour of the Ialugen group was reported according to both the physician and the patient (Pearson chi-square): $P < 0.01$ and $P < 0.05$, respectively.

Table 4
Global efficacy evaluation (%)

Score	Physicians		Patients	
	Ialugen	Placebo	Ialugen	Placebo
Poor	4.3	17.2	4.9	5.2
Fair	0.0	18.8	1.6	12.1
Good	31.4	25.0	24.6	39.6
Excellent	64.3	39.0	68.9	43.1
Statistics	$P < 0.01$		$P < 0.05$	

3.5. Tolerability assessment

The global tolerability results show that both treatments were very well tolerated. In fact, the majority of the patients and the investigators judged the tolerability of the test drugs to be 'good' or 'excellent' (Table 5). Four cases of side effects were registered in the PBO group (1 severe, 2 moderate and 1 light skin reaction). In the IA group, one case of light skin reaction was reported.

4. Discussion

Severe acute reactions are often observed during and after radiotherapy treatments. The use of new irradiation schedules as hyperfractionation or accelerated fractionation as well as multidisciplinary approaches combining synchronously radio- and chemotherapy are known to increase significantly both the risk and the severity of acute radio-epithelitis.

Besides its negative impact on patient's quality of life, the early onset of severe acute skin reactions during radiotherapy is often responsible for treatment interruptions and for a reduced compliance to the planned schedule of irra-

Table 5
Global tolerability (%)

Score	Physician		Patients	
	Ialugen	Placebo	Ialugen	Placebo
Poor	0.0	4.8	0.0	1.8
Fair	0.0	0.0	0.0	0.0
Good	7.5	8.1	11.5	7.0
Excellent	92.5	87.1	88.5	91.2
Statistics	$P = 0.18$		$P = 0.42$	

diation. Protocol violations and prolonged overall treatment time can account for an increased risk of local recurrence as demonstrated in patients with head and neck cancers [7].

The application on the skin of creams with corticosteroids can reduce the severity of dry epithelitis but their efficacy appears questionable when skin reaction becomes exudative or in case of ulcer. It is therefore justified to investigate the role of new compounds that could reduce the incidence and severity of acute toxicity of ionizing radiation on skin, to improve both the quality of life and the compliance of the patients to treatment constraints.

One of the most important physico-chemical properties of hyaluronic acid, which is found in relatively high physiologic concentrations in the human body, lies in its ability to retain more water than any other natural or synthetic polymer. An example of non-newtonian liquid, this compound is also characterized by its rheological nature and a viscosity which dramatically increases even at relatively low concentrations [8].

Hyaluronic acid has been shown by various research teams to stimulate and accelerate healing mechanisms during the three main phases of this process. During the hemostatic phase (present, in case of large, exudative radioepithelitis or skin ulceration), the combination of hyaluronic acid to fibrin generates a mechanical support favouring the migration of cells involved in repair mechanisms [15]. During the inflammatory phase, it stimulates the migration of macrophages and granulocytes to the damaged tissues, with a significant impact on phagocytosis. Finally, the phase of granulation is accelerated through its effects on repair processes such as the fibroblast migration and proliferation, collagen synthesis and endothelial cell proliferation [12-15].

Beyond the fact that the prophylactic use of a hyaluronic acid cream appears to slightly delay the onset of acute skin reactions (from week 1 in the PBO group to week 2 in the IA arm), it significantly decreases their intensity, both during ($P < 0.01$) and after ($P < 0.05$) radiotherapy. Likewise, at the time of the peak reactions (at week 5, in this study), the ratio between PBO and IA acute radioepithelitis, with score >1 , exceeds 3:1.

The therapeutic effect of Ialugen, also demonstrated by a separate analysis of the subgroup of patients developing severe acute reactions, scored 4 or 5. In the IA group, only one severe skin reaction was observed and healed within 1 week. This contrasts with the longer healing times (mean value 2.25 weeks) observed in the PBO group. This, together with the fact that, after the completion of the radiotherapy treatment, the incidence of radioepithelitis with scores >1 decreased more rapidly in the IA than in the placebo group, indicates that hyaluronic acid also accelerates healing of irradiated skin.

The global judgement, both by the physician and the patient, on the therapeutic efficacy and the tolerability of

the two treatments confirmed the results of the sequential assessment of acute skin reaction scores.

5. Conclusions

In this randomized, double-blind, placebo-controlled study carried out in 134 patients presenting with head and neck, breast or pelvic carcinomas, and treated with fractionated radiotherapy, the application of Ialugen cream on the irradiated skin area during radiation therapy was shown to postpone the first signs of acute epithelitis and reduce the severity of the skin reactions. Moreover, the fact that time to recover was longer, especially for the extensive exudative epithelitis and ulcers, in patients treated with placebo cream, indicates that hyaluronic acid was effective not only as a prophylactic but also as a therapeutic measure, as already proven in ulcers of different origins like *ulcus cruris* or *decubitus ulcers*, where this compound is successfully used to accelerate granulation tissue formation and the re-epithelialisation process. The results of this prospective study suggest an interesting role of the hyaluronic acid cream as supportive treatment to improve compliance and quality of life in patients undergoing radiation therapy.

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