A Phase II Randomized Study of Topical Intrarectal Administration of Amifostine for the Prevention of Acute Radiation-Induced Rectal Toxicity

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Purpose: To investigate the cytoprotective effect of intrarectal amifostine administration on acute radiation-induced rectal toxicity.
Patients and Methods: 67 patients with T1b–2 N0 M0 prostate cancer were randomized to receive amifostine intrarectally (group A, n = 33) or not (group B, n = 34) before irradiation. Therapy was delivered using a four-field technique with three-dimensional conformal planning. In group A, 1,500 mg amifostine was administered intrarectally as an aqueous solution in a 40-ml enema. Two different toxicity scales were used: EORTC/RTOG rectal and urologic toxicity criteria along with a Subjective-RectoSigmoid (S-RS) scale based on the endoscopic terminology of the World Organization for Digestive Endoscopy. Objective measurements with rectosigmoidoscopy were performed at baseline and 1–2 days after the completion of radiotherapy. The area under curve for the time course of mucositis (RTOG criteria) during irradiation represented the mucositis index (MI).
Results: Intrarectal amifostine was feasible and well tolerated without any systemic or local side effects. According to the RTOG toxicity scale, five out of 33 patients showed grade 1 mucositis in group A versus 15 out of 34 patients with grade 1/2 in group B ($p = 0.026$). Mean rectal MI was 0.3 ± 0.1 in group A versus 2.2 ± 0.4 in group B ($p < 0.001$), while S-RS score was 3.9 ± 0.5 in group A versus 6.3 ± 0.7 in group B ($p < 0.001$). The incidence of urinary toxicity was the same in both groups.
Conclusion: Intrarectal administration of amifostine seems to have a cytoprotective efficacy in acute radiation-induced rectal mucositis. Further randomized studies are needed for definitive therapeutic decisions.

Key Words: Randomized · Amifostine · Intrarectal · Radiotherapy

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Topische intrarektale Verabreichung von Amifostin zur Verhinderung akuter rektaler Strahlentoxizität: eine randomisierte Phase-II-Studie

Ziel: Untersuchung des zytoprotektiven Effekts von intrarektal verabreichtem Amifostin zur Verhinderung akuter rektaler Strahlentoxizität.
Patienten und Methodik: 67 Patienten mit einem Prostatakarzinom im Stadium T1b–2 N0 M0 wurden randomisiert zwei Gruppen zugeteilt: Gruppe A (n = 33) mit und Gruppe B (n = 34) ohne intrarektale Verabreichung von Amifostin vor der Bestrahlung. Zur Behandlung wurde eine Vier-Felder-Technik mit dreidimensionaler konformaler Bestrahlungsplanung eingesetzt. Die Patienten in Gruppe A erhielten 1500 mg Amifostin intrarektal als wässrige Lösung in einem 40-ml-Klysma. Zwei verschiedene Toxizitätsskalen wurden verwendet, die rektalen und urologischen Toxizitätskriterien der EORTC/RTOG und die auf der endoskopischen Terminologie der WODE (World Organization for Digestive Endoscopy) basierende S-RS-Skala („Subjective-RectoSigmoid scale"). Mittels Rektosigmoidoskopie wurden objektive Messungen vor und 1–2 Tage nach der Beendigung der Strahlentherapie durchgeführt. Der Bereich unter der Kurve (AUC) für den zeitlichen Verlauf einer Mukositis (RTOG-Kriterien) während der Bestrahlung stellte den Mukositis-Index (MI) dar.
Ergebnisse: Die intrarektale Verabreichung von Amifostin erwies sich als einfach und gut verträglich und führte zu keinen systemischen oder lokalen Nebenwirkungen. Gemäß der RTOG-Toxizitätsskala zeigten fünf von 33 Patienten der Gruppe A eine Mukosi-

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tis Grad 1 und 15 von 34 Patienten der Gruppe B eine Mukositis Grad 1/2 (p = 0,026). Der mittlere rektale MI betrug in Gruppe A 0,3 ± 0,1 gegenüber 2,2 ± 0,4 in Gruppe B (p < 0,001), während der S-RS-Score in Gruppe A bei 3,9 ± 0,5 gegenüber 6,3 ± 0,7 in Gruppe B lag (p < 0,001). Toxische Wirkungen an den Harnwegen traten in beiden Gruppen gleich häufig auf.
Schlussfolgerung: Die intrarektale Verabreichung von Amifostin scheint bei akuter strahleninduzierter Entzündung der Rektumschleimhaut zytoprotektiv zu wirken. Weitere randomisierte Studien sind erforderlich, um definitive Therapieentscheidungen treffen zu können.

Schlüsselwörter: Randomisiert · Amifostin · Intrarektal · Strahlentherapie

Introduction

The close proximity of the target volume of prostate tumors to the anterior rectal wall makes it impossible to totally eliminate the dose to the rectal wall. Rectal toxicity is often dose-limiting during pelvic radiation therapy [3, 8, 18]. Since conformal radiotherapy in pelvic tumors has the objective to reduce irradiation to organs at risk such as the rectum [15, 16], it is important to evaluate the side effects as comprehensively as possible. Endoscopy is considered to give the best estimation of moderate rectal mucosal damage, which does not inevitably lead to clinically evident proctitis [11]. Furthermore, proven prophylactically effective local or systemic therapies of radiation-induced rectal toxicity do not exist [31].

Amifostine (Ethyol; Schering-Plough Pharmaceuticals), an organic triphosphate, was the first cytoprotective drug to enter clinical practice [26]. It has already been approved for use as a radioprotector in the USA and the European Union, after publication of an important multicenter randomized study in head and neck cancer patients [4]. As cytoprotective agent for normal tissues against irradiation has been entered already in clinical practice and certain guidelines have been reported for its use [10]. In a previous publication, the cytoprotective efficacy of amifostine against radiation-induced mucositis in the rectal mucosa has been analytically studied using toxicity scales as well as endoscopic objective findings [13]. A possible strategy to permit safe dose escalation is the use of a radioprotector locally administered in the rectal mucosa. Initial animal experiments demonstrated that topical administration of the radioprotector WR-2721 (amifostine, Ethyol) on the rectal surface results in high concentrations of WR-2721 and its dephosphorylated active metabolite WR-1065 in the rectal mucosa [2, 21]. Another phase I trial showed the clinical efficacy and cytoprotective effect against late rectal toxicity of amifostine administered as an enema before radiotherapy [1]. Thus, we conducted a phase II trial to investigate, in a prospective randomized way, the cytoprotective effect of intrarectal administration of amifostine in the rectal mucosa.

Patients and Methods

A total of 67 cancer patients with prostate cancer were entered into this randomized phase II study between June 2002 and July 2003. Patients were randomly assigned to undergo radiotherapy supported with either intrarectal administration of amifostine (group A) or no cytoprotection (group B), according to a table of random numbers (0 vs. 1). Patients' characteristics are listed in Table 1. All patients had prostate cancer with T1b–2 stage of disease.

Recruitment Criteria

Patients recruited onto the study had a Karnofsky performance status > 70 and were referred for radical radiotherapy. Written informed consent was obtained from all patients. The study of intrarectal administration was approved by the local ethics committee. Patients previously treated with radio- or chemotherapy or showing hemoglobin levels < 11 g/dl or white blood cell (WBC) counts < 2,500/μl and platelet counts < 100,000/μl were excluded. Patients with major heart, lung, liver, renal, or neurologic/psychiatric disease, and patients with hematologic malignancies were also excluded, as were patients showing serum creatinine or liver enzyme serum levels > 1.5 and 2.5 times the normal values, respectively. Patients with hyper- or hypotension were eligible for inclusion in the protocol. Patients with clinically evident pulmonary insufficiency or confirmed allergy were not excluded.

Pretreatment and Treatment Evaluation

Baseline studies included physical examinations, chest X-rays, blood counts with differential and platelet counts, complete

Table 1. Patients' characteristics and area under the curve for dose-volume histogram (AUC-DVH) per randomization arm. No significant differences were noted between the two arms.

Tabelle 1. Patientencharakteristika und Bereich unter der Kurve für das Dosis-Volumen-Histogramm (AUC-DVH) in den Randomisierungsgruppen. Es wurden keine signifikanten Unterschiede zwischen den beiden Gruppen festgestellt.

	Randomization arm		
	Group A (n = 33)	Group B (n = 34)	p
Age	67.1 ± 3.5	67.9 ± 4.2	0.71[a]
Location, stage			
• Prostate, T1b	12/33	14/34	0.82[b]
• Prostate, T2	21/33	20/34	
AUC-DVH	79.1 ± 4.8	78.5 ± 5.4	0.65[a]

[a] Mann-Whitney U-test
[b] Fisher's exact test

biochemical profiles, and ECGs. Pretreatment upper/lower abdomen computed tomography (CT) scans were obtained in all patients. Complete blood cell count, serum urea and creatinine levels as well as liver enzyme levels were assessed once every 2 weeks during the radiotherapy period and for 4 weeks thereafter. The symptomatology related to urinary toxicity was evaluated according to RTOG toxicity criteria [6]. In order to minimize the bias, the rectal toxicity was evaluated using two toxicity scales by two independent observers. The first investigator used the RTOG toxicity criteria. The objective findings of acute rectal toxicity were assessed and scored using a Subjective-RectoSigmoid (S-RS) toxicity scale described in detail in a previous publication [13]. The objective measurements for the latter scale were coming from flexible rectosigmoidoscopy performed at baseline and 1–2 days after the completion of radiotherapy schedule. Acute rectal or bladder toxicity according to RTOG scale and subjective items of modified SOMA scale were monitored once a week during treatment. The independent observers were blind without knowing the randomization arm for each case of evaluation.

During treatment, the maximum monitored RTOG toxicity grade per patient was recorded as the radiation-induced acute toxicity score. Beyond this, in order to monitor the radiation-induced morbidity by time, we also performed a mucositis index (MI) for rectal and urinary toxicity as described below according to the trapezoid function [20]:

$$MI = \sum_{i=1}^{n} \frac{(x_n - x_{n-1})(y_{n-1} + y_n)}{2}$$

where x = week(s) of treatment post-baseline, y = toxicity grade according to RTOG criteria, n = certain time point of measurements. The MI represents the area under curve (AUC) for the time course of mucositis during the whole treatment schedule. The same result would come also with the summation of the areas constituted by the triangles formulating the "trapezoid" curve of the time course of toxicity.

Radiotherapy Schedule and Treatment Planning

Table 1 lists the disease stages for each patient category. Radiation treatment planning was based on recent CT scans. A standard fractionation regimen was used in all cases (2 Gy/fraction, five fractions per week). A 6-MV linear accelerator was used for irradiation of all patients recruited. They were treated in supine position with a four-field-box technique using parallel opposed anterior and posterior and parallel opposed lateral portals with individualized blocks derived from beam's eye view. Dose was prescribed at the ICRU reference point at the intersection of the beams. Total dose was 70 Gy. In all patients, a three-dimensional treatment planning was performed in conjunction with dose-volume histograms (DVHs) for the target and the rectum (organ at risk) as well. The AUC of DVH for rectum was calculated for every patient. For these purposes, paper printouts of the DVH curve were digitized using an 8-bit resolution scanner connected to a PC. The automatic registration and segmentation of the border of AUC DVH as well as measurements of the AUC-DVH (in cm^2) were performed in the same way as described in the previous report [13]. The appropriate scaling factor was adjusted (10 cm = 100% of prescribed dose at x-axis and 10 cm = 100% of delineated rectum volume at y-axis) to ensure reproducibility and comparability between different plots.

Immediately after documentation of mucositis grade 3 (incontinence and cramping), the radiotherapy was interrupted until the grade of mucositis regressed to 1. The supportive care was homogeneous in the two groups. Patients with severe diarrhea were treated with loperamide. Moist skin care was administered in both groups to prevent radiation-induced dermatitis [22].

Amifostine Intrarectal Administration

Amifostine 1,500 mg was reconstituted in normal saline solution to bring the volume of the enema to 40 ml. The enema was administered 20–30 min before irradiation, and the patient stayed in bed for 2 min thereafter to ensure the drug remained intrarectally. Amifostine was administered for all days of treatment concerning group A patients. The enema was administered through a folley-nelatron catheter of 14 G.

Statistical Analysis

Statistical analysis was performed using the SPSS 8.0 package (SPSS, Chicago, IL, USA). χ^2-test and Fisher's exact test for 2×2 tables were used to test relationships between categorical tumor variables [27]. Statistical comparisons between mean values were done with the non-parametric Mann-Whitney U-test [27]. Bonferroni correction for multiple tests was also used [24]. A p-value < 0.05 was considered significant.

Results

Amifostine-Related Toxicity

Amifostine was generally well tolerated. In group A, all patients completed therapy without showing amifostine-related toxicity. Only two patients complained of discomfort and a prickly sensation in the anal canal on every intrarectal administration, but eventually, the symptoms were related to internal hemorrhoids. The application was feasible and well tolerated, while the enema remained in the rectal-anal canal for nearly 2 h without producing any symptom of nonpreferable bowel movement.

Radiation-Induced Toxicity

The distribution of maximum acute radiation-induced rectal and urinary toxicity grade is shown in Table 2. None of the patients had grade 3 or 4 toxicity. According to the RTOG toxicity scale, the overall incidence of radiation morbidity grade of rectal was significantly lower in group A. In detail, five out of 33 patients (15.2%) showed grade 1 mucositis in group A as compared to 15 out of 34 patients (44.1%) with grade 1/2 in group B (p = 0.026). In group A, 84.8% of patients had no mucositis versus

55.9% in group B (p = 0.015, Fisher's test). However, the incidence of urinary toxicity grade 1/2 was equal in both groups in terms of ten out of 33 patients (30.3%) in group A versus nine out of 34 (26.5%) patients in group B (p = 0.76), while two patients in group A and three patients in group B experienced grade 2 toxicity with nycturia and dysuria requiring an anesthetic. In terms of MI, as shown in Table 3, the mean rectal MI was significantly lower in group A with 0.3 ± 0.1 versus 2.2 ± 0.4 in group B (p < 0.001). Additionally, the statistical significance of the differences between groups A and B concerning rectal MI and S-RS scores was inside the criterion of Bonferroni correction for multiple tests (p = 0.017). Figure 1 shows a significant difference in the AUC for the mean value of MI stratified per group, concerning rectal mucositis (p < 0.001). No significant difference was noted between groups A and B in terms of the mean value of MI for urinary toxicity. Rectosigmoidoscopy revealed more severe rectal mucositis in group B. The mean score for rectal toxicity deriving from S-RS scale (subjective and objective findings) was significantly lower in group A, where it amounted to 3.9 ± 0.5 as compared to 6.3 ± 0.7 in group B (p < 0.001). Concerning the AUC-DVH, no significant differences were assessed between the two groups (Table 1), confirming the homogeneity of the study in terms of the irradiated rectal volume.

Table 2. Incidence of radiation-induced genitourinary and lower gastrointestinal toxicity (maximum monitored grade) according to RTOG acute radiation morbidity scoring criteria.

Tabelle 2. Inzidenz der strahleninduzierten urogenitalen und gastrointestinalen Toxizität (höchster festgestellter Grad) nach den RTOG-Kriterien.

Toxicity grade	Grade 0	Grade 1	Grade 2
Urinary	None	Frequency of urination or nycturia twice pretreatment habit Dysuria, urgency not requiring medication	Frequency of urination or nycturia which is less frequent than every hour Dysuria, urgency, bladder spasm requiring local anesthetic
Group A	23/33	8/33	2/33
Group B	25/34	6/34	3/34
Pooled over grade: p = 0.76 (χ^2)			
Lower gastrointestinal	None	Increased frequency – change in quality of bowel habits not requiring medication Rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs Mucous discharge not necessitating sanitary pads Rectal or abdominal pain requiring analgesics
Group A	28/33	5/33	–
Group B	19/34	13/34	2/34
Pooled over grade: p = 0.026 (χ^2)		Grade 0 vs. 1 and 2: p = 0.015 (Fisher's test)	

Discussion

The mechanism by which amifostine exerts its selective protection of normal tissue is based on the ability of free thiol to be taken up in higher concentrations in normal organs than in tumor tissue. The differential uptake of WR-1065 is due to differences in the microenvironment at the tissue level resulting in the slow entry of the free thiol into tumor masses [5, 26]. Tumors are relatively hypovascular, thus resulting in tissue hypoxia, anaerobic metabolism, and a low interstitial pH. The combined hypovascularity and low pH result in low rates of prodrug activation by alkaline phosphatase. In addition, the distribution of alkaline phosphatase in normal and malignant tissue differs, with higher concentrations of this enzyme found in capillaries and arterioles of normal cells and lower levels of alkaline phosphatase observed in tumor tissue. Thus, selective protection is afforded normal tissues by reduced metabolism of amifostine to the active protector WR-1065 and low uptake of WR-1065 by tumors [30]. The end result is as much as a 100-fold higher steady concentration of the free thiol in normal organs such as bone marrow, kidney, salivary glands, and heart, compared with tumor tissue. Once the free thiol WR-1065 has entered a normal cell, it is available to bind directly to, and thus detoxify, the active species of alkylating agents, platinum agents, or ionizing radiation [25].

Randomized studies have already shown that there is clinical evidence for cytoprotection [4, 10, 13, 29]. Several publications have investigated the specific cytoprotective effect of amifostine on radiation-induced toxicity in pelvic irradiated areas. Liu et al. [17] reported the results of a randomized clinical study conducted in China that evaluated the use of amifostine and radiotherapy in 100 patients with locally advanced rectal cancer. Patients were randomized to treatment with daily fractionated irradiation with or without amifostine.

Table 3. Mean values of mucositis index (MI) according to the RTOG scale and Subjective-RectoSigmoid (S-RS) scale stratified by group.

Tabelle 3. Mittelwerte des Mukositis-Index (MI) nach der RTOG-Skala und der subjektiven Rektosigmoid-Skala (S-RS) für die einzelnen Behandlungsarme.

	Group A (n = 33)	Group B (n = 34)	p[a]
Genitourinary RTOG MI	2.1 ± 0.9	2.2 ± 1.1	0.6
Lower gastrointestinal RTOG MI	0.3 ± 0.1	2.2 ± 0.4	< 0.001[b]
S-RS score	3.9 ± 0.5	6.3 ± 0.7	< 0.001[b]

[a] Mann-Whitney U-test

[b] statistical significance according to the actual α-level of 0.017 due to Bonferroni correction for multiple tests (z-value > 2.388 for double-sided testing)

Pretreatment with amifostine had a significant impact on the incidence of moderate or severe late toxicities (alterations in bladder or gastrointestinal mucosa): 0% (0 of 34 patients) in the amifostine and radiation therapy arm versus 14% (five of 37 patients) in the arm with radiation therapy alone ($p = 0.03$). In a nonrandomized trial of amifostine versus control, Dunst et al. [7] reported a significantly lower bowel toxicity (maximum diarrhea score 1.07 ± 1.03 vs. 0.40 ± 0.63; $p = 0.044$) in patients with rectal cancer undergoing postoperative pelvic irradiation with 50.4 Gy combined with amifostine, even if the drug was administered intermittently. Kouvaris et al., in a retrospective study, reported a significant cytoprotective efficacy of amifostine in patients under pelvic irradiation [12].

However, Kuechler et al. [14] analyzing the residual chromosomal damage in a subset of patients participating in the study of Dunst et al. [7], reported an increased amount of residual chromosomal damage in the group treated with amifostine as well as in that without amifostine. The first reason for this might be related to the high interindividual variation of chromosomes in the relatively small number of patients entered into the study: variation has quite an impact and could have masked a possible protective or modulating effect of amifostine. From another point of view, the lower time and dosage of administered amifostine in the study of Dunst et al. might not be sufficient to cause less chromosomal damage. Moreover, the chromosomal analysis took place 2–3 years after irradiation, and thus we may also consider that Kuechler et al. analyzed the possible radioprotective effect of amifostine against the late effects of radiotherapy, whereas Dunst et al. reported only on the acute effects.

The topical application of amifostine has been a challenge, since the intravenous or subcutaneous application of this substance is associated with systemic toxicity as already reported in the literature [10]. Montana et al. [23] reported on the efficacy of rectally administered amifostine admixed in a foam in patients receiving large pelvic field irradiation. The investigators used surviving crypts to score radiation damage but were not able to demonstrate any protection. However, in another preclinical trial, Ben-Josef et al. by studying the topical application of WR-2721 in the rectum of male Copenhagen rats, reported significantly high concentrations preferentially in the rectal wall [2]. The same authors further validated their preclinical results by reporting significant clinical benefit of endorectal amifostine administration in a phase I study [1]. Our results are in accordance with the above observations. Both of the two independent investigators have monitored significantly lower rectal toxicity in arm A. Not only the mean MI but also the severity of proctitis was significantly reduced, as shown in Tables 2 and 3. The objective evaluation using rectosigmoidoscopy revealed significant differences of mucosal toxicity between the two arms.

The results of the current study should be regarded as reliable for three main reasons. First, the randomized study design minimizes the danger of bias. Second, the acute radiation-induced toxicity was evaluated by blind investigators who were not aware of the randomization arm for each case under evaluation. And last but not least, radiation-induced rectal toxicity has a dose-volume-related effect [16, 19]. According to our analysis, no significant differences between amifostine and control arm were monitored in the AUC-DVH concerning the rectum as organ at risk, indicating that the impact of dose-volume effect on normal tissue complication probability (NTCP) was homogeneous between the treatment arms [18]. Boersma et al. [3] reported that 65 Gy to > 40% of the rectal wall volume would lead to an increasing probability of rectal bleeding. The latter report may probably explain the fact that no grade 4 toxicity (rectal bleeding) was tracked for all patients during the radiotherapy schedule, since due to conformal treatment planning the above limitations were not reached. Hartford et al. [9] reported that rectal bleeding was related to the dose and volume of the anterior rectal wall irradiated. The relative risk of bleeding was increased fivefold when 75 Gy was delivered to 30% of the rectal wall volume or when lower doses (65 Gy) were delivered to 70% of the rectal wall volume. Storey et al. [28] observed a statistically significant improvement in freedom from grade 2–3 rectal complications when the volume of rectum treated to doses > 70 Gy was kept to 25%.

In closing, the results of this study clearly demonstrate the feasibility and tolerability of this approach. Our patients had no difficulty retaining the daily enema in the supine, sitting, or upright position. The lack of systemic toxicity was complete and was explained by the lack of systemic absorption as reported in previous publications by Ben-Josef et al. [1, 2] as well as Menard et al. [21].

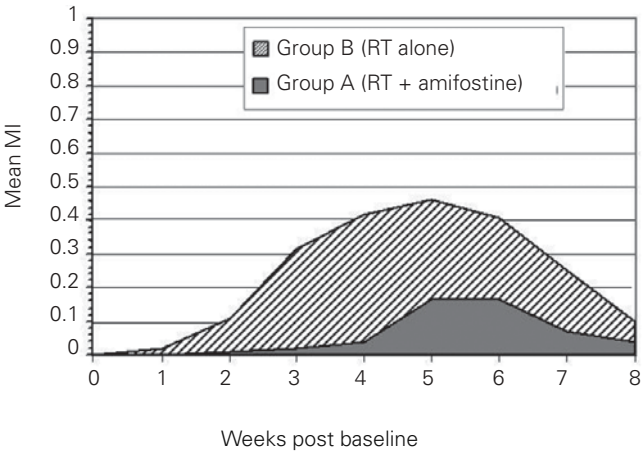

Figure 1. Mucositis index (MI) for rectal toxicity according to RTOG criteria calculated for group A (receiving amifostine) and B (without amifostine), representing the weekly mean values for each group ($p < 0.001$). RT: radiotherapy.

Figure 1. Mukositis-Index (MI) der rektalen Strahlentoxizität nach RTOG-Kriterien – berechnet für Gruppe A (unter Amifostin) und für Gruppe B (ohne Amifostin). Wiedergegeben sind die wöchentlichen Mittelwerte jeder Gruppe ($p < 0{,}001$).

The intrarectal administration of amifostine seems to have a cytoprotective effect on radiation-induced rectal mucositis. Beyond the small number of patients, this prospective randomized study has demonstrated that daily intrarectal administration of amifostine can successfully reduce the incidence and severity of acute rectal mucositis in pelvic irradiated areas, while the duration of mucositis as expressed by the MI is also significantly reduced. However, our results have also shown that intrarectal administration of amifostine has no effect on the cytoprotection of the urinary system. This can be easily explained by the lack of systemic absorption of intrarectally located WR-2721. Therefore, no cytoprotection in the bladder or urethra was taking place in group A. The potential cytoprotective effect of amifostine concerning late rectal toxicity should be also evaluated. Parallel to the current study, this work is already in progress concerning rectosigmoidoscopy 6 and 12 months after pelvic irradiation.

The current results should also serve as a stimulus to further clarify the cytoprotective effects of amifostine in future research projects. The answers will help further to define the role of this drug in clinical practice. Phase III randomized trials with more sufficient number of patients stand in need for further evaluation and confirmation of the best way of administering amifostine in patients undergoing pelvic irradiation. We may also propose the intrarectal administration of amifostine in patients with systemic reactions related to amifostine. However, the fact that there is no cytoprotection to the urinary system should not be underestimated, since the only cytoprotection noted in our study was concerning the rectal mucosa.

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