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ORIGINAL ARTICLE

Retrospective evaluation of the safety of low-level laser therapy/photobiomodulation in patients with head/neck cancer

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Abstract

Background The standard therapeutic approach for locally advanced head and neck cancer is optimal use of radiation therapy with or without concomitant chemotherapy. The most common and distressing acute complication of such therapies is oral/pharyngeal mucositis that may be associated with severe morbidity and can interfere with the planned administration of therapy.

Methods We have identified all patients diagnosed with head/neck cancer between 2005 and 2009, having received radiotherapy with or without cisplatin-based chemotherapy. Radiotherapy consisted of intensity-modulated radiation therapy (IMRT) in all patients. In patients with grade > 2 mucositis, photobiomodulation (PBM) consisted of three sessions of low-level laser irradiation weekly, in accordance with recently published recommendations for PBM. Patients who did not receive PBM were those for whom that approach was not requested by the radiotherapists and those who declined it.

Results Two hundred twenty-two patients (62%) received PBM and 139 did not (39%). The patient's characteristics were equally distributed between the two groups. For overall survival, time to local recurrence, and progression-free survival, there was no statistical evidence for a difference in prognosis between patients with and without PBM. In a multivariate analysis, after adjusting for known prognostic factors, we found no statistical evidence that PBM was related to overall survival, progression-free survival, or local recurrence.

Conclusions Our results show evidence of no effect of PBM upon overall survival, time to local recurrences, and disease-free survival of patients with head and neck cancer treated with radiotherapy with/without chemotherapy.

Keywords Laser therapy · Photobiomodulation · Oral mucositis · Prevention · Head/neck cancer · Radiotherapy

Introduction

The standard therapeutic approach for locally advanced head and neck cancer is optimal use of radiation therapy with or without concomitant chemotherapy, as primary treatment or after surgery; this approach results in a long-term survival without recurrence in at least 35% of the patients [1].

The most common and distressing acute complication of such therapies is oral/pharyngeal mucositis, occurring virtually among all mucosal regions where the total dose of radiotherapy exceeds 50 Gy [2–5]. The toxicity associated with combined modality treatment approach remains a major problem [6]. This is often the case as the standard dose to the high-risk zone is 60 to 66 Gy and 70 Gy in the postoperative and the primary setting, respectively.

Mucositis can cause severe and debilitating pain, requiring opioid analgesics and interfering with food intake, thus often necessitating enteral and/or parenteral nutrition [7]. There is

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also an increased infection risk due to rupture of normal mucosal barriers. As a consequence, the quality of life of most patients is markedly decreased. Moreover, mucositis can interfere with the planned administration of therapy, which may jeopardize the ultimate clinical outcome. Finally, mucositis often results in an increased cost of therapy through the need for hospitalization and/or special care [8].

Until recently, many supportive interventions were only symptomatic and most had serious limitations [9]. The low-energy laser therapy for the prevention and treatment of radiation-induced mucositis was introduced in 1999 by Bensadoun and co-workers [10]. Its remarkable effectiveness was confirmed by others [11] but, only recently, this technique (now called photobiomodulation (PBM)) has been widely adopted and officially included into practice guidelines for the management of mucositis secondary to cancer therapy [12] [13] [14].

The understanding of the pathogenesis of oral mucositis is still not complete but points to a multi-factorial nature of this inflammatory condition with many interrelated events in multiple tissue compartments [15]. The biological mechanisms responsible for the efficacy of PBM have not been fully elucidated either, although there is evidence that PBM enhances wound healing, reduces inflammation and pain, and prevents fibrosis [16]. Given all these biological complexities, it is not surprising that the question of safety of PBM has been raised, especially regarding a potential detrimental role on tumor risk progression, tumor behavior, or tumor response to curative multimodal therapeutic approach [17]. These most important aspects have been comprehensively discussed by Zecha et al. [18]. Although there are still more questions than answers regarding these issues, the authors concluded that it seems highly unlikely that PBM by itself represents a carcinogenic threat.

Because it appears unlikely that the final answer to the PBM tumor-related neutrality will be exclusively provided by laboratory or animal studies, we undertook the present retrospective analysis of our head/neck cancer patients who underwent both radiation therapy and PBM management, comparatively with those treated without PBM, aiming to evaluate clinically the outcome of cancer therapy results over a significant period of follow-up.

Patients, material, and methods

In the Bordet Cancer Registry, we have identified all patients diagnosed with head/neck cancer between 1/1/2005 and 31/12/2009, without a history of a previous malignancy, and having received radiotherapy at the Institut Jules Bordet.

Radiation therapy has been performed at the Institut Bordet for all patients, but some patients were afterwards followed by the referring physicians outside the Institut Bordet.

The technique of radiotherapy consisted of intensity-modulated radiation therapy (IMRT) in all patients. IMRT plans were made with the inverse sliding window treatment planning module and delivered on Varian linear accelerator with dynamic multi-leaf collimation. The prescribed dose to the non-involved lymph node levels was 50 Gy in 25 fractions in 5 weeks. The PTV of the tumor and of the high-risk lymph node levels was planned to receive 60–66 Gy in 6–6.5 weeks in the post-operative setting and 70 Gy in 7 weeks in case of incomplete resection and in patients who received definitive IMRT, all in fractions of 2 Gy. When used concomitantly with radiotherapy, chemotherapy consisted of platinum-based agents (mostly high-dose tri-weekly cisplatin regimen) according to international guidelines [19]. The follow-up of the oral cavity was done by the radiation oncologist, assisted by a stomatologist or the physician in charge of the PBM, if indicated.

PBM consisted of three sessions of low-level irradiation weekly using a Biophoton Travelers Oncolase TW scanning laser combining a visible 100 mW laser and IR laser with power of 50, 250, and 500 mW. A patient was included in the group having received PBM if PBM was started within 3 months after initiation of radio (chemo)therapy. This laser irradiation was achieved through an optic fiber with a spot size of about 1 cm^2; the fiber tip was maintained 5–10 mm above the lesions. The irradiation was continuous. The median treatment duration of PBM was 1 month. The treatment time (t) for each application point was given by the equation: $t(s)$ = energy density (J/cm^2) × surface (cm^2)/power (W). Actually, the wavelength used was 630 nm and the power output was 100 mW. During the sessions, patients wore wavelength-specific dark glasses to protect their eyes.

The average energy density delivered to the treatment areas was 2–3 J/cm^2 and was applied to all sites, equally distributed on the treated surfaces, for a calculated mean duration of 33 s per site (each session lasted approximately 6 min). This is in accordance with recently published recommendation for PBM as a management for oral mucositis [20].

PBM was applied intraorally. The treatment areas included the inferior and superior lips, right and left cheeks, right and left tongue, palate and velum palate, right and left gingiva, and the tongue frenulum. However, the site of the tumor itself was not illuminated, according to the local drawings provided by the radiation oncologist.

Patients were treated with PBM in case of grade > 2 mucositis according to the WHO score. Patients who did not receive PBM were those for whom the approach was not requested by the radiotherapists and those who declined it.

Statistical methods

Differences in continuous variables between patients with PBM and without were assessed with the Wilcoxon test; differences

Table 1 Patients characteristics

	All patients ($N = 361$)		No PBM ($N = 139$)		PBM ($N = 222$)		p value
Age							
Mean ± std	59 ± 11		59 ± 13		59 ± 10		0.83
Gender							
Female	91	25%	32	23%	59	27%	0.45
Male	270	75%	107	77%	163	73%	
Smoker before diagnosis							
No	27	10%	8	8%	19	11%	0.47
Yes	252	90%	92	92%	160	89%	
Missing info	82		39		42		
Smoker at diagnosis							
No	93	33%	28	28%	65	36%	0.15
Yes	188	67%	73	72%	115	64%	
Missing info	80		38		42		
Alcohol use							
No	51	19%	21	23%	30	17%	0.22
Yes	215	81%	69	77%	146	83%	
Missing info	95		49		46		
cT							
is	2	< 1%	1	< 1%	1	< 1%	0.43
1	46	16%	25	24%	21	11%	(Tis, T1, T2 vs T3, T4)
2	103	35%	31	30%	72	38%	
3	72	24%	20	19%	52	27%	
4	72	24%	28	27%	44	23%	
Missing info	66		34		32		
cN							
0	121	35%	65	52%	56	26%	< 0.001
1	80	23%	22	18%	58	27%	(0 vs > 0)
2	124	36%	32	26%	92	42%	
3	17	5%	5	4%	12	6%	
Missing info	19		15		4		
cM							
0	340	96%	130	96%	210	97%	0.57
1	13	4%	6	4%	7	3%	
Missing info	8		3		5		
Tumor localization							< 0.001
Lip and oral cavity	56	16%	18	13%	38	17%	
Lip	1		1		–		
Oral cavity	55		17		38		
Pharynx	188	52%	55	40%	133	60%	
Nasopharynx	37		11		26		
Oropharynx	113		24		89		
Hypopharynx	38		20		18		
Larynx	100	28%	57	41%	43	19%	
Nasal cavity and paranasal sinuses	8	2%	5	4%	3	1%	
Major salivary glands	9	2%	4	3%	5	2%	
Chemotherapy							
No	139	39%	79	57%	60	27%	< 0.001
Yes	222	62%	60	43%	162	73%	
Surgery							
No	248	69%	85	61%	163	73%	0.02
Yes	113	31%	54	39%	59	27%	
Diagnosis (D), treatment (T), and follow-up (FU)							
D, T, and FU at Institut Bordet (IB)	51	14%	13	9%	38	17%	0.07
D outside IB, T at IB	128	35%	55	40%	73	33%	
D at IB/T at IB and outside IB	1	< 1%	1	< 1%	–	–	
D outside IB/T at IB and outside IB	181	50%	70	50%	111	50%	

in categorical variables were assessed with the chi-square or Fisher Exact test. Overall survival (OS) is defined from date of diagnosis till date of death. Patients alive at last follow-up were censored at the date of last follow-up. Time to local recurrence was defined as time to local relapse or locoregional relapse. Patients without local/locoregional relapse at their last follow-up were censored at that date. Progression-free survival (PFS) was defined as time to locoregional relapse, distant metastasis, or death, whatever occurred first. If no PFS event occurred by the date of last follow-up, patients were censored at

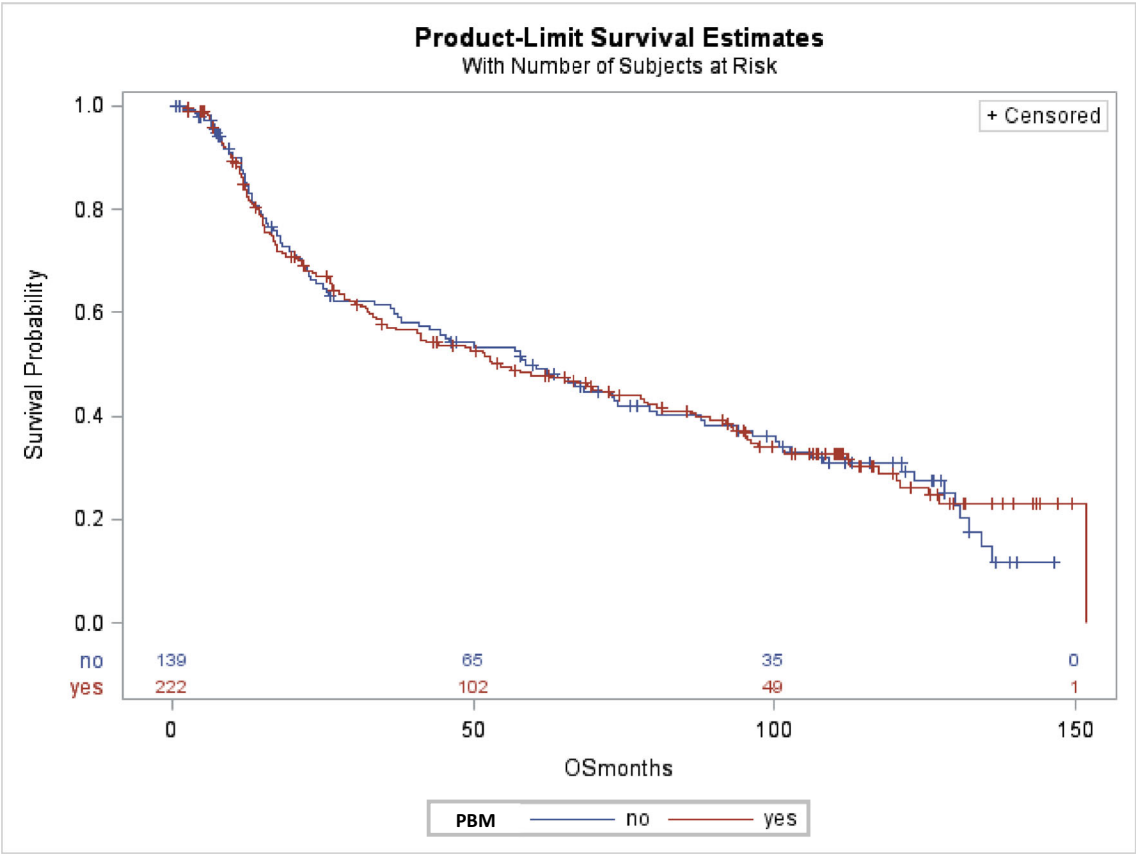

Fig. 1 Overall survival

that date. Kaplan-Meier curves were constructed to visualize the difference in OS, time to local recurrence, and PFS between patients with and without PBM. The logrank test was used to compare the Kaplan-Meier curves. Hazard ratios and their 95% confidence limits were calculated using Cox's proportional hazards model. The median follow-up was calculated by the Reverse Kaplan-Meier method. Multivariate analyses were performed in order to assess the effect of PBM on (1) OS, (2) time to local recurrence, and (3) PFS, by adjusting for age, gender, smoker before diagnosis (yes/no), smoker at diagnosis (yes/no), alcohol use (yes/no), cT (T3,T4 vs lower), cN (0 vs > 0), cM (yes/no), tumor localization, chemotherapy (yes/no), and surgery (yes/no). We have performed variable selection of the adjusting factors (keeping only those factors in the model that reached statistical significance). All statistical analyses were performed by using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

The sample size was limited by the available patient population. From a preliminary analysis, we expected to select around 500 patients (230 with PBM and 270 without). With a minimum theoretical follow-up of more than 5 years, we expected to get at least 45% of PFS events, i.e., an absolute number of 225 events. With this number of events, we were able to detect, if true, a hazard ratio of 0.65 (two-sided test, power of 90%).

Information about progression status and life status was sought during summer 2018.

The ethical committee of the Institut Jules Bordet gave a formal approval to conduct this retrospective analysis.

Results

Actually, 361 patient's charts were available; 222 patients (62%) received PBM and 139 did not (39%). The patient's characteristics are shown in Table 1. The following parameters were equally distributed between the two groups: age, gender, smoking before and at diagnosis, and alcohol use. The staging of the tumor (TNM) was also roughly comparable between the two groups of patients, except for N0 which was more frequent in the non-PBM group (52%) than in the PBM one (26%) ($p < 0.001$).

There was also a difference between the two groups in the proportions of patients receiving chemotherapy in addition to radiotherapy: 73% and 43% ($p < 0.001$) of the PBM treated and non-treated patients, respectively, had concomitant chemotherapy. Non-operated patients more often received PBM than operated patients: 66% (163/248) vs 52% (59/113) ($p = 0.02$).

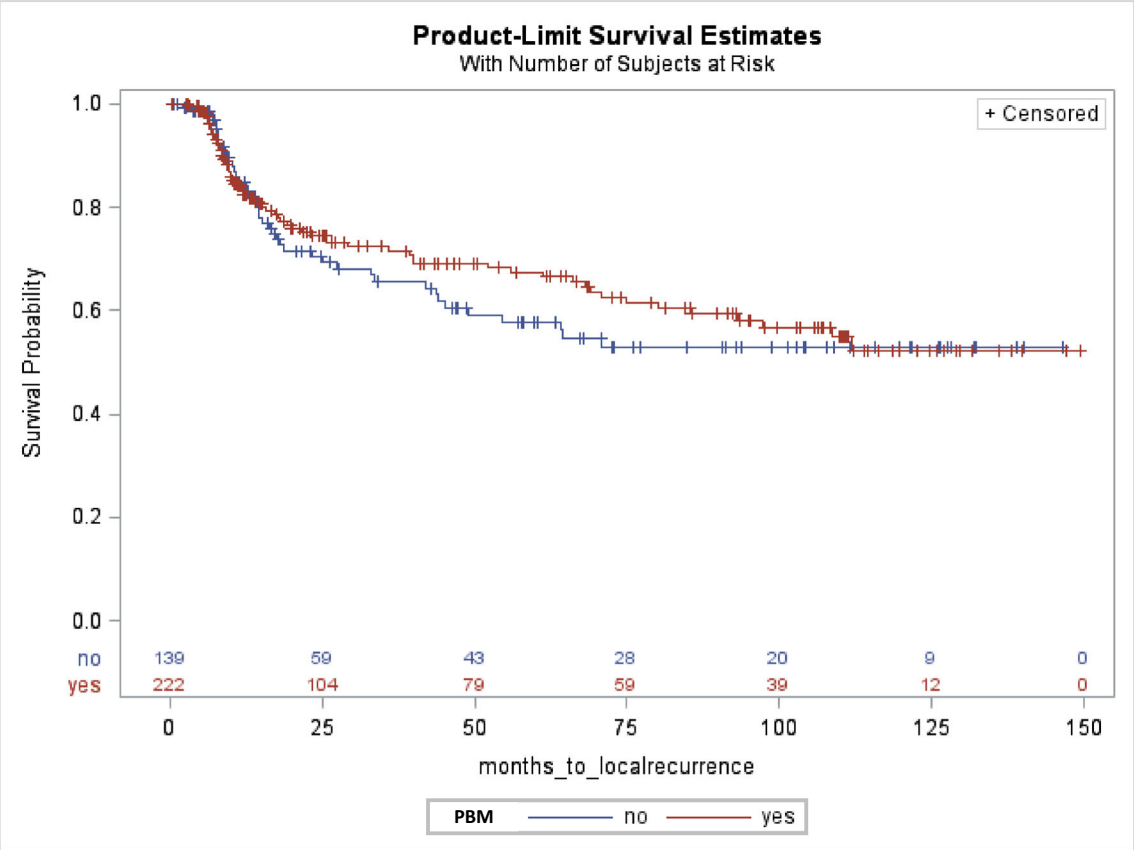

Fig. 2 Time to local recurrence

Overall survival ($N = 232$ events) is shown in Fig. 1, time to local recurrence ($N = 111$ events) in Fig. 2, and PFS ($N = 250$ events) in Fig. 3. Median follow-up was 9.3 years (95% CI, 8.9 to 9.7). Seventy-five patients had date of last news anterior to 01/07/2017 (i.e. more than 1 year before the date of data search). In all three time-to-event distributions, there was no statistical evidence for a difference in prognosis between patients with and without PBM: (1) OS, hazard ratio 0.98 (95% CI, 0.75 to 1.27), p value 0.86; (2) time to local recurrence, hazard ratio 0.88 (95% CI, 0.60 to 1.29), p value 0.52; and (3) PFS, hazard ratio 0.92 (0.71 to 1.18), p value 0.49.

A multivariate analysis was performed after adjusting for the following parameters: age, gender, smoking before diagnosis (yes/no), smoking at diagnosis (yes/no), alcohol use (yes/no), tumor size (is, T1, T2, T3, T4), nodal status (0 vs > 0), presence of metastases at diagnosis (yes/no), tumor localization, chemotherapy (yes/no), and surgery (yes/no). We performed a stepwise selection of the adjusting factors but kept the variable PBM in the model. The results are shown in Table 2.

Even after adjusting for known prognostic factors, there is no statistical evidence that PBM is related to overall survival, progression-free survival, or local recurrence. Because in some patients, who were followed after their treatment outside the Institut Bordet, we might have missed the registration of local relapse or occurrence of metastases, we have redone the analysis for the patients who had their treatments and follow-up done exclusively at the Institut Jules Bordet (179 patients). The results are shown in Table 3. Also in this sub-population, there is no statistical evidence that PBM could be related to overall survival, time to local recurrence, or progression-free survival (Table 4).

Discussion

We conducted a retrospective analysis of patients treated for locally advanced head/neck cancers with radiotherapy (with or without chemotherapy) who received or not PBM (low-level laser treatment) for the prevention or management of therapy-induced mucositis. We could not find any statistical evidence that PBM might be related to overall survival, progression-free survival, or time to local recurrence.

Clearly, the first prerequisite for any supportive measure in cancer medicine is that it does not adversely affect tumor behavior or response to treatment, a possibility that has been raised by Sonis et al. [17], on the basis of laboratory observations. However, it seems unlikely that PBM has carcinogenic effects or might protect cancer cells from cancer treatment, as discussed comprehensively by Zecha et al. [18]; although,

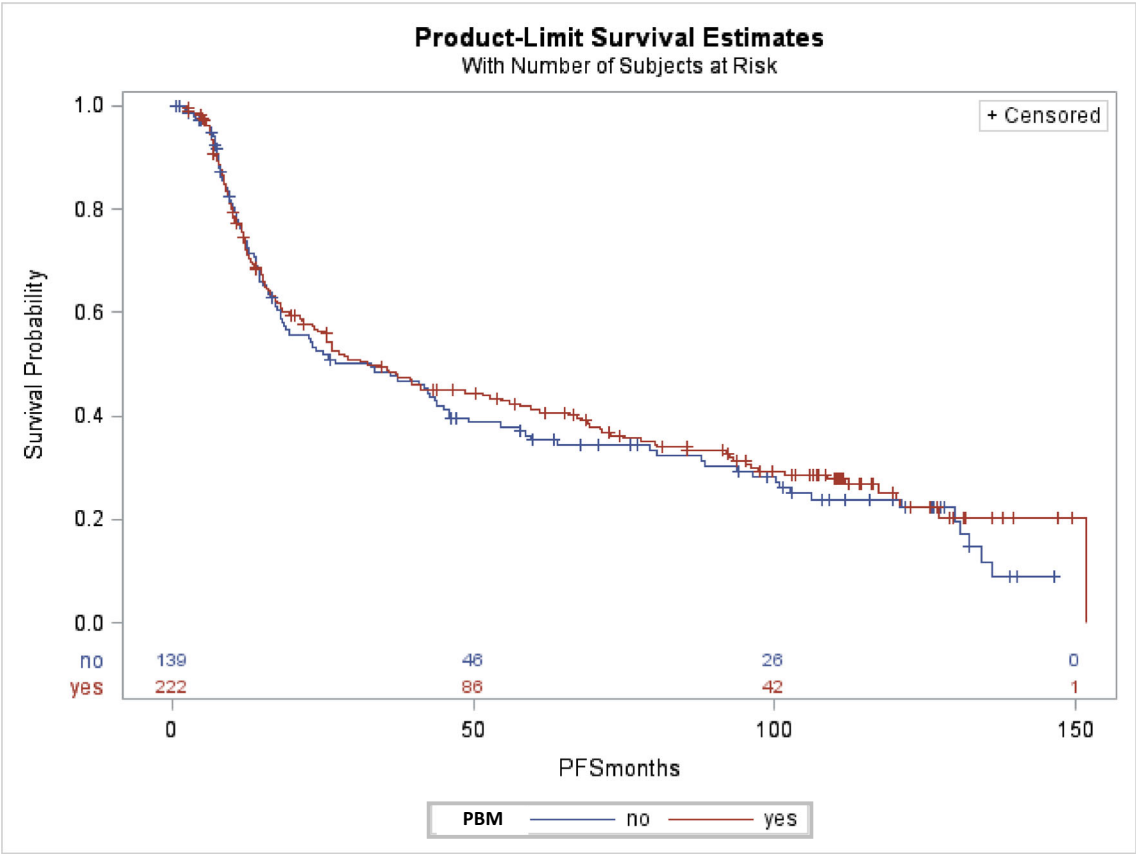

Fig. 3 Progression-free survival

some recent ex vivo experiments suggest a possible adverse effect of PBM on head/neck cancer cell [21]. Actually, some recent laboratory observations suggest that PBM might sensitize cancer cells to radiation [22] or increase apoptosis [23], both being potentially promising strategies that could be applied in the clinic.

Nonetheless, it is clear that robust recommendations for clinicians about the use of PBM in cancer patients cannot be based on laboratory data only. Clinical prospective studies are highly needed.

Recently, Brandão et al. [24] reported on 152 patients with advanced oral squamous cell carcinoma who received both

Table 2 Multivariate analysis

Hazard ratio PBM vs no:
- Overall survival, 0.81 (95% CI, 0.59 to 1.12); *p* value 0.20
- Time to local recurrence, 0.99 (95% CI, 0.65 to 1.52); *p* value 0.96
- Progression-free survival, 0.76 (95% CI, 0.56 to 1.04); *p* value 0.09

Adjusting for age, gender, smoker before diagnosis (yes/no), smoker at diagnosis (yes/no), alcohol use (yes/no), cT (T3,T4 vs lower), cN (0 vs > 0), cM (yes/no), chemotherapy (yes/no), and surgery (yes/no) and perform stepwise variable selection on the adjusting factors.
- For predicting OS, only smoker before diagnosis and cT reached statistical significance as adjusting factors (to PBM) in the multivariate model
- For predicting time to local recurrence, only smoker at diagnosis reached statistical significance as adjusting factor (to PBM) in the multivariate model
- For predicting PFS, only smoker before diagnosis and cT reached statistical significance as adjusting factors (to PBM) in the multivariate model

Table 3 Sensitivity analysis

Univariate hazard ratio, PBM vs no:
- Overall survival, 1.08 (95% CI, 0.74 to 1.60); *p* value 0.69
- Time to local recurrence, 0.79 (95% CI, 0.48 to 1.31); *p* value 0.37
- Progression-free survival, 0.89 (95% CI, 0.62 to 1.27); *p* value 0.51

Multivariate hazard ratio, PBM vs no:
- Overall survival, 1.10 (95% CI, 0.73 to 1.65); *p* value 0.66
- Time to local recurrence, 0.92 (95% CI, 0.52 to 1.61); *p* value 0.77
- Progression-free survival, 0.95 (95% CI, 0.64 to 1.40), *p* value 0.80

Adjusting for age, gender, smoker before diagnosis (yes/no), smoker at diagnosis (yes/no), alcohol use (yes/no), cT (T3,T4 vs lower), cN (0 vs > 0), cM (yes/no), chemotherapy (yes/no), and surgery (yes/no) and perform stepwise variable selection on the adjusting factors.
- For predicting OS, only smoker before diagnosis reached statistical significance as adjusting factor (to PBM) in the multivariate model
- For predicting time to local recurrence, only smoker at diagnosis reached statistical significance as adjusting factor (to PBM) in the multivariate model
- For predicting PFS, only smoker before diagnosis reached statistical significance as adjusting factor (to PBM) in the multivariate model

Table 4 Five-year overall results

	No PBM ($N = 139$)	PBM ($N = 222$)
5-year overall survival	50%	48%
5-year local recurrence-free survival	58%	67%
5-year progression-free survival	35%	41%

radiation therapy and PBM; the patients were analyzed retrospectively and compared with historical controls. The authors concluded that PBM did not impact treatment results, recurrence, or survival.

A prospective randomized trial by Antunes et al. in a total of 94 head and neck cancer patients receiving concurrent chemoradiation and PBM to prevent oral mucositis [25] has been recently updated with respect to long-term survival [26]. With a median follow-up of 41 months, the patients who received PBM had a statistically significant better complete response to treatment and increased progression-free survival as well as a tendency for better overall survival.

Our study supports these observations in terms of non-inferiority of PBM vs no PBM for overall survival, disease-free survival, and time of local recurrence interestingly, in analogy with Antunes et al. [26]

Our study has some strong aspects. Firstly, it has been done on a relatively large number (361) of patients with a median follow-up of 9.3 years. Second, it has been conducted in patients who all received radiation therapy and PBM in the same institution using techniques that were not substantially modified during the observation period (2005–2009).

We must also recognize weaker points in our study. First, it is a retrospective analysis with all the implications of such an approach compared with prospectively randomized trials; however, it might be difficult to conduct future controlled studies in this field because it would now be unethical to deny PBM—an officially recommended procedure [12]—to some patients. Due to the retrospective nature of the study, we are facing some imbalances between groups: the patients without PBM had more frequently N_0 tumors and, consequently, have less frequently received chemotherapy. Those imbalances are not surprising as in N_0 tumors, less mucosa might have been irradiated up to high doses and chemotherapy was required less frequently in these patients with less advanced tumors. However, these imbalances are not extremely worrying as it means that the group without PBM was expected to have a better prognosis than the other group. This expectation suggests that our conclusions are not biased in the direction of an underestimation of a potential deleterious effect of PBM as we rather observed that this is the group with PBM who has the better observed rates of PFS and OS. However, to conclude to a favorable synergistic effect of PBM with anti-cancer therapy is a further step that we do not want to make with the non-randomized design of our study. The failure to detect differences in overall survival is only an argument to conclude to the safety of PBM. One might fear that some patients were refuted for chemotherapy because of comorbidities preventing them to receive chemotherapy and putting them therefore at worst prognosis: this fear is not justified by the observed data as the patients who were not administered chemotherapy do better than the other patients (data not shown). Second, we probably need a confirmation from larger numbers of patients: we anticipated the observation of 225 PFS events and we actually got 250. Nevertheless, this does not improve much the capability of the study to detect a HR of 0.65 or less with 90% power. This means that we were not able to statistically detect an impact on survival that might be considered clinically important. However, prospective studies would require a prolonged time for recruitment and a long follow-up, during which therapeutic techniques may change. An alternative might be a large multicenter retrospective study.

To conclude, from our results, there is no argument to believe that PBM for cancer therapy–induced oral mucositis might negatively affect the overall survival, time to local recurrence, and disease-free survival of patients with head and neck cancer who were receiving radiotherapy (with or without chemotherapy). Our conclusions certainly deserve confirmation; nonetheless, we feel that, at this stage, oncologists can use PBM for the management of therapy-induced oral mucositis in head and neck cancer patients without fearing to jeopardize the final outcomes of cancer therapy as there is no evidence of a detrimental long-term effect.

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Compliance with ethical standards

The ethical committee of the Institut Jules Bordet gave a formal approval to conduct this retrospective analysis.

Conflict of interest The authors declare that they have no conflict of interest.

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