Background: Aloe vera has been widely used to treat various conditions such as sunburn or radiation-related dermatitis, mucositis, or esophagitis. It is suggested that Aloe vera may be beneficial for radiation-induced mucositis.

Objective: To evaluate the efficacy of oral aloe vera juice in the alleviation of radiation-induced mucositis in head and neck cancer patients using a double-blind, randomized controlled trial.

Methods and materials: Sixty-one eligible head and neck cancer patients, who received conventional radiation therapy at Ramathibodi Hospital, were randomized to receive oral Aloe vera juice or placebo. Mucosal reaction was assessed during the course of radiation using the Radiation Therapy Oncology Group grading system.

Results: Patient baseline characteristics were identical in Aloe vera juice and placebo groups except in the gender. The incidence of severe mucositis was significantly lower in the Aloe vera group compared with the placebo group (53% vs. 87%, p = 0.004). However, there was no significant difference in the time-duration to severe mucositis development. No adverse effects related to the drug were observed.

Conclusion: Oral aloe vera juice was beneficial in alleviating the severity of radiation-induced mucositis and without side effects. The Aloe vera juice may be an alternative agent treating radiation-induced mucositis in patients with head and neck cancers.

Keywords: Aloe vera, head and neck cancer, radiation-induced mucositis.
settings. Patients were required to have Karnofsky performance status of more than 70. The patients who had prior irradiation of the head and neck, history of allergy to Aloe vera, underlying diabetes mellitus, and HIV-positive were excluded from this study.

**Study design**

The study was designed as a double-blind randomized, placebo controlled trial. The protocol was approved by Ethics Committee of Ramathibodi Hospital. All patients gave informed consent before randomization. The randomization was performed using stratified block randomization. Patients were stratified on the basis of concurrent chemotherapy because concurrent chemotherapy might worsen the degree of radiation-induced mucositis.

The allocation was concealed and blinded to physician, patients, and personnel involved in the study. After randomization, the patients were assigned to two groups: Aloe vera juice and placebo group. The physicians instructed patients to take a 15 mL of the solution three times daily, beginning on the first day and continuing throughout the three-four weeks of the radiation course and continuing to the end of the 8th week follow-up.

Aloe vera juice and placebo was provided by the Aloe vera research group of the Faculty of Pharmacy, Mahidol University. Aloe vera juice consisted of 80% aloe juice, 0.2% preservative, 0.001 % lemon-lime flavor, and sweetened with sorbitol. The placebo solution was taste-matched, with identical astringency, consistency, and ingredients, but the Aloe vera juice was replaced with water.

Conditioning therapy and supportive care were administered according to a standard institutional practice, alleviating oral discomfort by rinsing daily with water, normal saline and viscous lidocaine, analgesic drugs and antibiotics were allowed. Feeding tubes were used when patients could not eat.

**Radiation therapy**

Standard radiation technique with cobalt-60, 6 or 10 MV x-rays or any combination of these megavoltage beams was used. The treatment fields included >50% of the oral cavity, oropharynx or both. The radiation dose was a total dose of 50-70 Gy, using standard fractionation of 1.8-2 Gy once a day.

**Study endpoints and patient evaluation**

Between July 2008 to January 2009, 61 patients with head and neck cancers were enrolled into the study at the Radiotherapy and Oncology unit, Ramathibodi Hospital. There were 30 patients in the Aloe vera group and 31 patients in the placebo group. Due to difficult recruitment of suitable patients, we decided to report our data before achieving the predetermined total sample size of 80.

The primary end point was the onset and incidence of the severe mucositis. Severe mucositis was defined as the Radiation Therapy Oncology Group (RTOG) mucositis grade 2, 3, and 4. The onset of severe mucositis was defined as the time-duration from the first day of radiation to the day when the observer recorded the most severe mucositis. The secondary data collected for the study were the percentage of weight loss, the number of the patients and duration of radiation break due to mucositis, analgesic, antibiotics, and antifungal drug requirement for mucositis treatment and adverse events. The percentage of weight loss was defined by [(Weight of the last day of radiotherapy) – (Weight t of the first day of radiotherapy)] / (Weight of the first day of radiotherapy) x100 (%).

Baseline mucosa status was performed within 10 days prior to the first day of radiation therapy. During radiation treatment, visual signs of mucositis were assessed two times per week by two radiation oncologists. After the complete course of radiation, the patients were assessed at the last radiation day and were asked to come for OPD visits for mucosal assessment at week 2 and 4 post-radiation. The mucositis grading was followed using the RTOG grading system as shown in Table 1. At completion of radiation, patients were requested to return all bottles so that compliance with the study could be assessed.

**Statistical analysis**

Sample size was calculated using a log-rank test [2], so that an overall sample size of 79 patients might attain at 80% power achievement at a 0.05 significance level to detect a difference of 30% between the median onset of severe mucositis development in groups 1 and 2, respectively. Efficacy analysis was based on the intention-to-treat basis. Demographic and baseline characteristics of the patients in each treatment group was presented using descriptive statistics and compared using chi-square or t-test according to type of the data. Logistic regression analysis was performed to evaluate predictive factors for mucositis.
The efficacy of oral Aloe vera juice for radiation-induced mucositis

outcome. The time-duration to severe mucositis development was analyzed by Kaplan-Meier test. The log-rank test was used to compare the outcome between both groups. Multivariate analysis was performed using the Cox proportional hazard model. Data analysis was performed with commercial statistical software (SPSS for windows version 13.0).

Results

The baseline characteristics of patients, natured of tumors, and treatments are summarized in Table 2-4. These characteristics did not differ significantly between the two groups, but there were more male patients in the Aloe vera group (p=0.03) and more previous surgery cases in the placebo group (p=0.04).

One patient in the placebo arm discontinued the test solution due to unfavorable taste and was reported as a non-compliance. No patients reported adverse effect or withdrew from the study.

The incidence of severe mucositis is summarized in Table 5. Apparently, patients in the aloe vera group had a lower incidence of severe mucositis than patients in the placebo. This was statistically significant. (53% vs. 87%, p=0.004).

Table 1. Acute mucositis scoring: RTOG grading system.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>no change over baseline.</td>
</tr>
<tr>
<td>1</td>
<td>injection, might experience mild pain not requiring analgesic</td>
</tr>
<tr>
<td>2</td>
<td>patchy mucositis that produces an inflammatory serosanguinous discharge, might experience moderate pain requiring analgesic.</td>
</tr>
<tr>
<td>3</td>
<td>confluent fibrinous mucositis; might include severe pain requiring narcotics</td>
</tr>
<tr>
<td>4</td>
<td>ulceration, hemorrhage, necrosis.</td>
</tr>
</tbody>
</table>

Table 2. Patient characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Aloe vera group (n=30)</th>
<th>Placebo group (n=31)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Male (number; %)</td>
<td>27 (90)</td>
<td>20 (65)</td>
<td></td>
</tr>
<tr>
<td>Female (number; %)</td>
<td>3 (10)</td>
<td>11 (35)</td>
<td></td>
</tr>
<tr>
<td>Age (year; min-max)</td>
<td>60 (38-91)</td>
<td>54 (31-84)</td>
<td>0.18</td>
</tr>
<tr>
<td>Previous smoking (number; %)</td>
<td>24 (80)</td>
<td>17 (55)</td>
<td>0.056</td>
</tr>
<tr>
<td>Duration of smoking (year; min-max)</td>
<td>30 (4-70)</td>
<td>28 (6-51)</td>
<td>0.47</td>
</tr>
<tr>
<td>Alcohol consuming (number; %)</td>
<td>20 (74)</td>
<td>16 (57)</td>
<td>0.26</td>
</tr>
<tr>
<td>Duration of consuming (year; min-max)</td>
<td>27 (4-40)</td>
<td>25 (4-45)</td>
<td>0.5</td>
</tr>
<tr>
<td>Previous surgery (number; %)</td>
<td>4 (13)</td>
<td>12 (38)</td>
<td>0.04</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td>0.35</td>
</tr>
<tr>
<td>No</td>
<td>13 (43)</td>
<td>13 (42)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17 (57)</td>
<td>18 (58)</td>
<td></td>
</tr>
<tr>
<td>Weight before radiation (kg; min-max)</td>
<td>51 (38-74)</td>
<td>55 (39-82)</td>
<td>0.3</td>
</tr>
<tr>
<td>Karnofsky performance status (number; min-max)</td>
<td>90 (70-100)</td>
<td>90 (70-100)</td>
<td>0.35</td>
</tr>
</tbody>
</table>
Table 3. Tumor characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Aloe vera group (n=30)</th>
<th>Placebo group (n=31)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary tumor site</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharynx (number; %)</td>
<td>7 (23)</td>
<td>6 (19)</td>
<td>0.11</td>
</tr>
<tr>
<td>Oropharynx (number; %)</td>
<td>8 (27)</td>
<td>6 (19)</td>
<td></td>
</tr>
<tr>
<td>Hypopharynx (number; %)</td>
<td>5 (17)</td>
<td>2 (7)</td>
<td></td>
</tr>
<tr>
<td>Oral cavity (number; %)</td>
<td>3 (10)</td>
<td>12 (39)</td>
<td></td>
</tr>
<tr>
<td>Larynx (number; %)</td>
<td>6 (20)</td>
<td>2 (7)</td>
<td></td>
</tr>
<tr>
<td>Nasal cavity/paranasal sinus (number; %)</td>
<td>1 (3)</td>
<td>2 (7)</td>
<td></td>
</tr>
<tr>
<td>Unknown primary (number; %)</td>
<td>0</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma (number; %)</td>
<td>28 (94)</td>
<td>28 (91)</td>
<td>0.56</td>
</tr>
<tr>
<td>Adeno carcinoma (number; %)</td>
<td>0</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Adenoid cystic carcinoma (number; %)</td>
<td>0</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated carcinoma (number; %)</td>
<td>1 (3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Others (number; %)</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor staging</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (number; %)</td>
<td>3 (10)</td>
<td>5 (16)</td>
<td>0.83</td>
</tr>
<tr>
<td>T2 (number; %)</td>
<td>8 (28)</td>
<td>8 (26)</td>
<td></td>
</tr>
<tr>
<td>T3 (number; %)</td>
<td>6 (21)</td>
<td>6 (19)</td>
<td></td>
</tr>
<tr>
<td>T4 (number; %)</td>
<td>12 (41)</td>
<td>11 (36)</td>
<td></td>
</tr>
<tr>
<td>Unknown (number; %)</td>
<td>0</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td><strong>Nodal staging</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0 (number; %)</td>
<td>8 (28)</td>
<td>13 (42)</td>
<td>0.22</td>
</tr>
<tr>
<td>N1 (number; %)</td>
<td>7 (24)</td>
<td>2 (7)</td>
<td></td>
</tr>
<tr>
<td>N2 (number; %)</td>
<td>9 (31)</td>
<td>12 (39)</td>
<td></td>
</tr>
<tr>
<td>N3 (number; %)</td>
<td>5 (17)</td>
<td>4 (13)</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Treatment characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Aloe vera group (n=30)</th>
<th>Placebo group (n=31)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previous surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(number; %)</td>
<td>4 (13)</td>
<td>12 (38)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13 (43)</td>
<td>13 (42)</td>
<td>0.35</td>
</tr>
<tr>
<td>Yes</td>
<td>17 (57)</td>
<td>18 (58)</td>
<td></td>
</tr>
<tr>
<td><strong>Radiation therapy dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cGy; min-max)</td>
<td>7000(5940-7200)</td>
<td>7000(5600-7200)</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Total treatment time</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(days)</td>
<td>52 (37-67)</td>
<td>51 (38-82)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Table 5. The incidence of severe mucositis.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Aloe vera group (n=30)</th>
<th>Placebo group (n=31)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe mucositis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(number; %)</td>
<td>16 (53)</td>
<td>27 (87)</td>
<td>0.004</td>
</tr>
</tbody>
</table>
The distribution of RTOG mucositis between the treatment groups was shown in Fig. 1. Binary logistic regression analysis was performed to evaluate predictive factors for the mucositis outcome. The use of Aloe vera was the only independent predictive factor for mucositis outcome (Aloe vera vs. placebo; OR=5.906; 95%CI= 1.656-21.066; p=0.006).

The Kaplan-Meier curves for the onset of severe mucositis are shown in Fig 2. There was no statistically significant difference between the two groups. The median onset of severe mucositis was 32 and 33 days for patients taking Aloe vera and patients assigned to take placebo, respectively (p= 0.609). The multivariate analysis using the cox proportional model was used to analyze the onset of severe mucositis controlled for each variable (gender, previous surgery, and previous smoking). It was confirmed that difference in these outcomes was not present between Aloe vera and placebo group.

Table 6 shows objective outcome of the treatment. Patients in the two groups had similar outcomes among a variety of other objectives. The patients in the Aloe vera group had a lower percentage of weight loss and radiation breaks due to mucositis than patients in the placebo arm but the difference was not statistically significant.

Fig. 1 Distribution of mucositis against RTOG grading in Aloe vera and placebo groups.

Fig. 2 The Kaplan-Meier curve of the onset of severe mucositis (grade II, III, IV).
Radiation-induced mucositis is a common and dose-limiting toxicity of RT among patients with head and neck cancers. A number of agents with different activation mechanisms have been used in the prevention and treatment of this condition [3], but there is still no widely-accepted prophylaxis or effective treatment available for this type of mucositis.

In Thailand, Aloe vera is used widely such as for protection and treatment of burns from sun. The Aloe plant contains multiple pharmacologically active compounds which have healing and anti-inflammatory effects. Up to date, clinical studies have reported the beneficial effects of Aloe gel in wound healing [4, 5], treatment of oral ulcers [6-8]. Several animal studies and clinical trials have assessed the effectiveness of Aloe gel in the treatment of skin burns [9, 10], skin exposure to Ultraviolet (UV) and Gamma radiation [11, 12], frostbite and psoriasis [13-15], anti-inflammatory effect [16, 17], immune-stimulating effect [18-22], antiviral and antitumor activity [23, 24].

The present result showed that Aloe vera did not delay the onset of severe mucositis compared with the placebo. Patients who received Aloe vera developed less mucositis with statistically significant difference from the placebo group. It was also confirmed that there was a significant association between Aloe vera treatment and lower mucositis grading. Interestingly, Aloe vera could only reduce the incidence of severe mucositis but could not delay the onset of severe mucositis. The discordant outcome might mean that the Aloe vera effect is not strong enough for mucositis prevention but adequate for alleviating and slowing down the progression of mucositis.

Su et al. [25] reported the use of oral Aloe vera for reduction of radiation induced mucositis in 200. It was shown that oral Aloe vera was not a beneficial adjunct to head and neck radiotherapy compared with placebo. The present results agree findings agree with the onset of mucositis, percentages of weight loss, the incidence of radiation break due to mucositis by Su et al, but our obtained incidence of severe mucositis was lower, indicating a statistically significant clinical benefit with Aloe vera use. Our findings might be explained by a difference in the preparation of our solution. In this study, we used a fresh Aloe vera gel prepared under well-controlled technique of enzyme deactivation. For this reason, our solution could preserve more essential active compounds, such as glycoprotein, which are powerful substances to promote healing and anti-inflammatory effects. According to Danhof et al. [26], fresh Aloe gel could promote dermal wound healing better than existing commercial products.

Limitations of our study were: 1) the relatively small number of patients, 2) a baseline characteristic imbalance, and 3) the difficulty to control patients’ compliance. Due to a slow recruitment, the present sample size was 60 patients. Nevertheless, this report of 60 patients could still detect some benefits of using Aloe vera solution in terms of a lower incidence of severe mucositis. In the present baseline characteristics, there were a disproportional by higher number of male patients in the Aloe vera group and

### Table 6. Objective outcome of the treatment.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Aloe vera group (n=30)</th>
<th>Placebo group (n=31)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Weight loss (mean±SD)</td>
<td>-5.0±6.2</td>
<td>-6.9±6.7</td>
<td>0.26</td>
</tr>
<tr>
<td>Radiotherapy break due to mucositis (number; %)</td>
<td>1 (3)</td>
<td>4 (13)</td>
<td>0.35</td>
</tr>
<tr>
<td>Duration of radiotherapy break (days)</td>
<td>7</td>
<td>12.0±6.7</td>
<td>0.53</td>
</tr>
<tr>
<td>Analgesic requirement (number; %)</td>
<td>15 (49)</td>
<td>18 (58)</td>
<td>0.44</td>
</tr>
<tr>
<td>Antibiotic requirement (number; %)</td>
<td>5 (17)</td>
<td>3 (10)</td>
<td>0.41</td>
</tr>
<tr>
<td>Antifungal requirement (number; %)</td>
<td>4 (13)</td>
<td>3 (10)</td>
<td>0.90</td>
</tr>
</tbody>
</table>
in more patients who had previous surgery in the placebo group. In order to overcome the bias due to
the patients’ heterogeneity, we attempted to minimize this using a stratified randomization method. With
chemotherapy use, we still could not avoid some inadvertent bias. We could not totally monitor the
patients’ compliance, but we reminded all patients on every visit to strictly follow the protocol.

The present study will be extended to a longer duration or extent of mucositis until the mucositis totally
disappears.

**Conclusion**

Oral Aloe vera juice had benefits in alleviating the severity of radiation-induced mucositis without
any side effects. In Thailand, Aloe vera is readily accessible and of relatively low cost. Aloe vera juice
should be considered as a good alternative agent for treating radiation-induced mucositis in patients with
head and neck cancers.

**Acknowledgement**

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participation.

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to report.

**References**

1. Sutherland SE, Browman GP. Prophylaxis of oral mucositis in irradiated head-and-neck cancer patients:


