

## Original Article

# Topical use of olive oil preparation to prevent radiodermatitis: results of a prospective study in nasopharyngeal carcinoma patients

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**Abstract:** Background: Radiodermatitis is a common side effect of radiotherapy. However, an effective method for the prevention of radiodermatitis has not yet been identified. The purpose of this study was to evaluate the effectiveness of topical olive oil in the prevention of acute radiodermatitis in patients with nasopharyngeal carcinoma (NPC) who were undergoing concurrent chemoradiotherapy. Methods: A prospective study was conducted in patients with NPC. The patients were randomized into the intervention (n = 47) and control (n = 47) groups. Patients in the control group were treated with a general skin care regimen (placebo), whereas patients in the intervention group were treated with olive oil thrice daily for 7 weeks during chemoradiotherapy and for two weeks thereafter. On a weekly basis for a total duration of 9 weeks, a blinded observer assessed the severity of dermatitis, which was graded from 0 to 4 according to the Radiation Therapy Oncology Group (RTOG) criteria and the Visual Analog Scale (VAS) score. Results: Mild reactions due to radiation (grades I and II) occurred in 93.6% of the intervention group and in 72.3% of the control group. Patients in the intervention group encountered significantly less severe dermatitis during chemoradiotherapy compared with patients in the control group ( $P < 0.01$ ). A multivariate analysis revealed that the use of olive oil ( $P < 0.01$ ) was significantly associated with a decrease in skin injuries. Conclusions: The prophylactic use of olive oil was associated with a significant decrease in the intensity of acute dermatitis in NPC patients. The results of this trial indicate that olive oil holds promise as a safe and effective prophylactic treatment for radiodermatitis.

**Keywords:** Radiodermatitis, nasopharyngeal carcinoma, olive oil

## Introduction

Radiotherapy (RT) has become an integral component of the complex treatment protocol for nasopharyngeal carcinoma (NPC). Irradiation of NPC is generally well tolerated; however, side effects that involve the skin are frequently encountered. The most frequent side effect of radiation is radiodermatitis, which is characterized by erythema, dry desquamation, moist desquamation, skin folds, and pitting, even to the extent of painful ulceration or necrosis. These side effects can affect patient quality of life and might cause pain and discomfort, limit activities, and even cause treatment delays [1]. These effects are quite concerning given the strong clinical and radiological evidence that

protraction of overall treatment time has adverse influences on the radiocurability of certain tumors in humans, particularly squamous cell carcinoma of the nasopharyngeal region. To improve the therapeutic ratio, the search is ongoing for an agent with prophylactic properties that can prevent acute radiation dermatitis [2-5].

Aside from a thorough cleaning of the skin and the prevention of local irradiation-induced trauma, there are no well-established protocols for the prevention of radiation-induced toxicity in the skin [6]. The effects of various topical treatments, including steroid and non-steroid creams [2], anti-inflammatory and antihistamine compounds, fatty ointments, aloe vera gel

**Table 1.** Comparison of the baseline characteristics between the two groups

| Characteristic     | Intervention group | Control group | P      |
|--------------------|--------------------|---------------|--------|
| Age (median)       | 56.3 ± 4.9         | 55.5 ± 7.6    | > 0.05 |
| Sex                |                    |               |        |
| Male               | 43                 | 45            | > 0.05 |
| Female             | 4                  | 2             | > 0.05 |
| Dose               | 70 Gy              | 70 Gy         |        |
| Clinical stage III | 39                 | 42            | > 0.05 |
| Clinical stage IV  | 8                  | 5             | > 0.05 |

[7], and chamomile and almond creams, have been examined [3]. However, only a few studies have demonstrated that these treatments have significant protective effects.

Olive oil has a long history of use as a home remedy for skin maladies. The chief active components of olive oil include oleic acid, phenolic constituents, and squalene. The primary types of phenolics include hydroxytyrosol, tyrosol, and oleuropein, which naturally occur at high levels in virgin olive oil and have antioxidant activity. Hydroxytyrosol, tyrosol, and oleuropein have been demonstrated to exert antimicrobial effects against several strains of bacteria that are involved in intestinal and respiratory infections [8, 9]. In addition, olive oil is a natural and safe lubricant. Many cosmetics also contain olive oil as a base [10]. One study noted that the abundance of squalene in oils in general indicates that olive oil may be promising for the treatment of individuals with seborrheic dermatitis, acne, psoriasis, and atopic dermatitis. Squalene is used as an antioxidant, moisturizer, and convenient vehicle for topical application of other substances [11]. Al-Waili reported that a mixture of honey, beeswax, and olive oil alleviates diaper dermatitis, psoriasis, and eczema by inhibiting the growth of *Staphylococcus aureus* and *Candida albicans* [12]. The effect of olive oil on radiodermatitis has not yet been reported; therefore, the current study was performed to evaluate this effect.

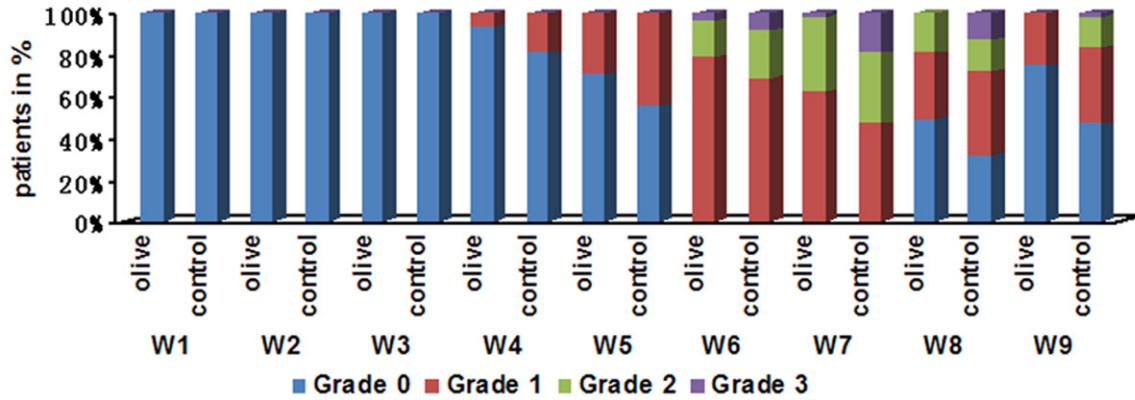
### Materials and methods

This randomized controlled study was conducted in Shandong province at the Qianfoshan Hospital Radiation Therapy Center. The study subjects were randomly assigned to two groups

according to a random number table. Patients with a histologically documented diagnosis of clinical stage III or IV NPC were eligible for this study. All participants were required to have received the same chemoradiotherapy regimen consisting of a 70-Gy total RT dose. Patients with a history of prior radiotherapy or with an allergy to olive oil were not included. For all patients, general recommendations for skin care were provided to minimize skin irritation, trauma, and infection. The recommended washing practices included gentle washing with water alone or gentle washing with mild soap and water, and the patients were advised to follow gentle washing practices with a mild shampoo. This study was approved by the Ethics Committee of Qianfoshan Hospital of Shandong Province, and all patients provided informed consent. Before beginning the study protocol, the patients were not informed about the type of treatment that they would receive. A total of 47 patients were randomly assigned to the prophylactic group; these patients were treated with olive oil thrice daily beginning on the first day of RT and continuing for 2 weeks after the completion of RT treatment. The control group consisted of 47 patients who were prophylactically treated with a general skin care regimen and with placebo (water) during RT and for 2 weeks after the completion of RT treatment. The primary treatment was high-dose RT with concurrent weekly cisplatin (25-30 mg/m<sup>2</sup>) and docetaxel (25-30 mg/m<sup>2</sup>).

The occurrence of side effects and adverse drug reactions was recorded by a dermatologist and a radiologist who were blinded to the study (i.e., they were unaware of the patient groupings, medications administered to the patients during the weekly clinical examinations, or the patients' chemoradiotherapy schedules). Radiation skin reaction scoring (grade 0: no changes; grade 1: light and/or painless erythema with desquamation and dryness; grade 2: sensitive and/or intense erythema with desquamation, partial sweating, and moderate edema; grade 3: widespread sweating and marked edema), which is used to assess erythema and desquamation, is widely accepted as the standard for the evaluation of skin reactions induced by radiation [15]. These scores also serve as the main index in our study. The primary signs of radiodermatitis (e.g., the intensity of erythema, the extent of dry and moist desquamation and necrosis, crusting exuda-

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**Figure 1.** Use of olive oil was associated with a significant decrease in the intensity of acute dermatitis in NPC patients. From the first to the third week, radioactive dermatitis was not observed in either the olive oil group or the control group. From the fourth to the fifth week, radioactive dermatitis was noted in some of the patients; however, the grade of inflammation in the experimental group was lower than that in the control group ( $P < 0.01$ ). From the sixth to the seventh week, radioactive dermatitis was noted in all of the patients. However, the grade of inflammation in the experimental group was not as low as that in the control group ( $P < 0.01$ ). From the eighth to the ninth week, patients in both the olive oil-treated group and the control group began to recover. However, the recovery level of the experimental group was significantly higher than that of the control group ( $P < 0.01$ ).

tion, and pain severity) as well as the radiodermatitis scores were recorded at least weekly during and after treatment. Factors that may cause skin reactions were documented (e.g., concomitant medication, age, cancer history, and concomitant diseases). Acute skin reactions were also documented according to the skin radiation morbidity scoring criteria of the Radiation Therapy Oncology Group (RTOG) [13]. Using Visual Analog Scales (VAS) to assess the symptoms (e.g., itching, pain, and burning) [14], a score of 0 was defined as “no symptoms”, and a score of 10 was defined as “the worst severity experienced”.

As RT treatment is dependent on the tumor stage, each patient was scheduled for RT including or excluding regional lymph node areas. An IMRT (TPS ECLIP10.0) treatment plan was calculated to administer a total dose of 70 Gy delivered in 2-Gy daily fractions over a period of 7 weeks. Irradiation was performed according to the criteria of the International Commission on Radiation Units and Measurements (ICRU).

### Statistical analysis

All data were analyzed using SPSS 17.0 statistical software. The baseline characteristics and reactions to radiation were compared between the two groups using chi-square tests. The

average RTOG score and the intensity of acute dermatitis between the two groups were compared using multivariate analyses. The mean VAS score was analyzed by applying t-tests.  $P$  values of  $< 0.05$  were considered statistically significant.

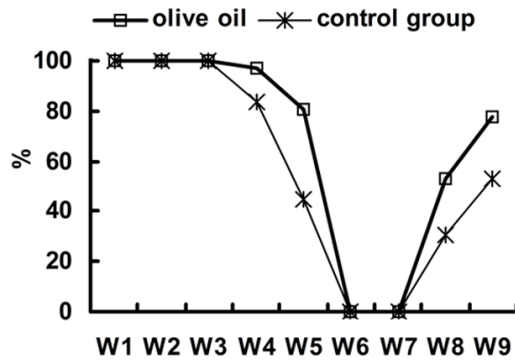
### Results

From January 2013 to June 2014, 94 patients were enrolled in the trial. As presented in **Table 1**, the two groups were similar in terms of their baseline characteristics. Patients with a histologically documented diagnosis of clinical stage III or IV NPC were eligible for this study. All participants were required to have received the same chemoradiotherapy regimen consisting of a total dose of 70 Gy. The age and gender of the patients and the clinical staging of the tumors did not significantly differ between the two groups.

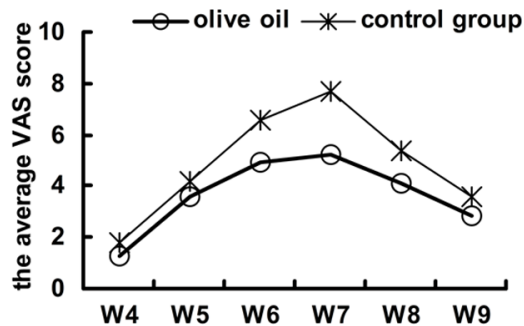
Radiodermatitis severity was assessed using the RTOG scale shown in **Figure 1**. Our multivariate analysis identified a significant benefit from the use of olive oil compared with the placebo during RT and follow-up ( $P < 0.01$ ).

Until the visit during week 3, all RTOG criteria were assessed as normal for all patients. From visit T6 to visit T7, 100% of the patients developed some degree of radiodermatitis (**Figures**

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**Figure 2.** The average RTOG score of the olive oil group was higher than that of the control group. From the fourth to the sixth week and the seventh to the ninth week. The average RTOG score of the olive oil group was higher than that of the control group ( $P < 0.01$ ).



**Figure 3.** The average VAS score of the olive oil group was lower than that of the control group ( $P < 0.01$ ).

1 and 2). None of the patients presented with grade IV radiodermatitis. The intervention group experienced significantly less severe dermatitis during RT compared with the control group. As expected, the severity of radiodermatitis increased with increasing doses of radiation (Figure 1). Our multivariate analysis revealed that the use of olive oil was associated with a significant benefit compared with placebo in the control group during both RT and follow-up ( $P < 0.01$ ).

The severity of radiodermatitis was assessed using the mean VAS score (Figure 3). The use of olive oil was associated with a significant benefit compared with the placebo administered to the control group during both RT and follow-up (t-test;  $P < 0.01$ ).

Until visit W6, the proportion of patients who did not develop radiodermatitis was significant-

**Table 2.** Radiodermatitis grades of patients in both groups

| Grade         | I-II | III | IV | P          |
|---------------|------|-----|----|------------|
| Olive oil     | 44   | 3   | 0  | $P < 0.05$ |
| Control group | 34   | 13  | 0  |            |

Chi-square ( $\chi^2$ ) test.

ly increased in the intervention group, and these results were statistically significant. The results as assessed by RTOG criteria are consistent with those assessed by VAS scores. At the end of the radiotherapy treatment, ulceration, hemorrhage, and necrosis were not observed in patients in either treatment group. Amelioration of symptoms upon the termination of radiation was observed in 74.4% (35/47) of patients using olive oil compared with 46.8% (22/47) of patients using a general skin care regimen.

Mild reactions to radiation (grades I and II) occurred in 93.6% (44/47) of patients in the intervention group and 72.3% (34/47) of patients in the control group. More severe reactions to radiation (grade III) were noted in 6.4% of patients in the intervention group and 27.7% of patients in the control group. A significant difference ( $P < 0.01$ ) was observed between the intervention and control groups (Table 2).

### Discussion

The most common side effect of radiotherapy in patients with NPC is radiation dermatitis, and numerous patients demonstrate grade 3 skin lesions before the scheduled end of RT. The severity of this acute toxicity is associated with (1) radiotherapy fraction schedules, (2) total dose, (3) treated skin area, (4) radiation energy, (5) radiation type (e.g., photon, electron), (6) volume of treated tissue, and (7) overall treatment (16). If cetuximab is administered simultaneously, an overlap of radiation- and cetuximab-induced skin reactions is observed in the radiation field, which may lead to severe skin toxicity [17]; indeed, more than 15% of patients develop a grade 3 or 4 skin rash [18, 19]. These side effects may reduce the patient's compliance and can be limiting factors with regard to adherence to RT protocols. Moreover, patients often experience anxiety related to the cosmetic appearance of the rash and may feel stigmatized, which can lead to psychosocial side effects that can negatively affect the qual-

ity of life of these patients [20]. Biafine, an oil-in-water emulsion with nonsteroidal anti-inflammatory properties, is commonly used to treat radiation-induced dermatitis, and its chemical composition has been described elsewhere [21]. Hamza demonstrated that trolamine cream can effectively reduce the intensity of acute dermatitis following 3-dimensional conformal radiation therapy (3D-CRT) with weekly cisplatin in patients with head and neck squamous cell carcinoma (HNSCC) [22]. However, Pommier compared calendula ointment with Biafine cream in 254 breast cancer patients and found that patients who were treated with calendula experienced significantly fewer occurrences of  $\geq$  grade 2 dermatitis ( $P < 0.001$ ) and greater pain relief ( $P = 0.03$ ) [21]. Therefore, more effective prophylactic treatments are urgently needed, especially for patients with NPC. This study was designed to assess whether supportive care with olive oil is effective in the prevention and reduction of acute radiation dermatitis compared with our standard skin care regimen based on various supportive care guidelines.

The first physiopathological step of radiation toxicity to the skin is an overproduction of free radicals, which are responsible for damage to the cells of the basal epidermal layer and endothelial cells [16]. Olive oil contains the monounsaturated fatty acid oleic acid as well as vitamin E and oleuropein [9]. The chemistry and physiological function of olive oil makes it a major antioxidant and anti-inflammatory agent. Squalene is used as an antioxidant, a moisturizer, and a convenient vehicle for topical application of other substances [11]. The abundance of squalene in oils in general underscores the promise of olive oil as a treatment for individuals with seborrheic dermatitis, acne, psoriasis, and atopic dermatitis. Ichihashi M found that daily topical use of extra virgin olive oil after sunbathing may delay and reduce UV-induced skin cancer development in human skin. One possible mechanism that might explain this effect is the finding that olive oil decreases the level of reactive oxygen species-induced 8-hydroxydeoxyguanosine, which is responsible for genetic mutations [23]. Panahi Y observed that an aloe vera/olive oil cream was at least as effective as 0.1% betamethasone in the treatment of sulfur mustard-induced chronic skin complications and might

serve as a promising therapeutic option for the alleviation of symptoms in patients exposed to mustard gas [24]. Moreover, olive oil is a natural and safe lubricant. Clinical experience suggests that the initial use of a plain, non-scented, lanolin-free hydrophilic cream would be helpful for patients with radiation-induced skin reactions. This type of cream attracts and traps moisture at the skin's surface to increase moisture and maintain skin pliability [25]. The use of olive oil is congruent with the opinions reflected in supportive care guidelines. As expected, the therapeutic effect of olive oil on acute dermatitis was superior compared with that of the general skin care regimen of the control group. These results, which were statistically significant, were congruent with the subjective toxicity assessment of patients using the VAS score; these results also provided evidence for the radioprotective effects of olive oil. Prior to this study, Kiechl-Kohlendorfer also demonstrated that topical skin therapy using olive oil cream lowers the risk of dermatitis. Olive oil cream was also superior to a water-in-oil emollient cream [26].

In our study, 100% of patients developed some degree of inflammation, such as erythema, dry or wet desquamation, skin folds, pitting, or edema, by the sixth week. The high incidence of radiodermatitis might depend on the absorbed dose and the area of irradiation [16]. Two weeks after the termination of radiation therapy, we observed that 77.8% of patients with radiodermatitis were cured, which could be attributed to the antioxidative and anti-inflammatory effects of olive oil. In addition, this effect might be attributed to the presence of linoleic acid, which influences skin physiology, skin barrier function, membrane fluidity, and eicosanoid production. In particular, linoleic acid is a component of the phospholipids of cell membranes as well as the ceramides in intercellular lipids that play a role in the barrier function of the skin [27, 28]. The ingredients in olive oil that possess anti-inflammatory and antioxidant properties have been considered good candidates for protection against radiodermatitis. Therefore, olive oil may be a promising and effective treatment for the prevention of acute skin lesions caused by RT in patients with NPC.

From the above results, we conclude that the prophylactic use of olive oil is associated with a significant decrease in the intensity of acute

dermatitis compared with a general skin care regimen in patients with NPC. The results of this trial demonstrate that olive oil is a promising, safe candidate prophylactic treatment option for radiodermatitis.

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### Disclosure of conflict of interest

None.

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