the Journal of CONTEMPORARY DENTAL PRACTICE at www.thejcdp.com
Volume 9 Number 3 March 1, 2008

The Effect of Topical Application of Pure Honey on Radiation-induced Mucositis: A Randomized Clinical Trial

M. Motallebnejad, DDS, MS; S. Akram, MD; A. Moghadamnia, PhD; Z. Moulana, MSc; S. Omidi, DDS

Abstract

Aim: Radiation-induced mucositis is an early effect of head and neck radiotherapy. Mucositis can cause ulcers, and patients may experience pain and dysphasia which need treatment. The aim of this study is to evaluate the effect of pure natural honey on radiation induced mucositis.

Methods and Materials: In this randomized single blind (examiner blind) clinical trial 40 patients with head and neck cancer requiring radiation to the oropharyngeal mucosa were randomly assigned to two groups. Twenty patients assigned to the study group received honey, while both the study and control groups received standard head and neck radiation therapy based on a standard protocol. In the study group patients were instructed to take 20 ml of honey 15 minutes before radiation therapy, then again at intervals of 15 minutes and six hours after radiation. In the control group patients were instructed to rinse with 20 ml of saline before and after radiation. Patients were evaluated weekly for progression of mucositis using the Oral Mucositis Assessing Scale (OMAS). Data were analyzed using the independent t-test, Mann-Whitney, and Friedman tests.

Results: A significant reduction in mucositis among honey-received patients compared with controls (p=0.000) occurred.

Conclusion: Within the limits of this study the results showed the application of natural honey is effective in managing radiation induced mucositis.

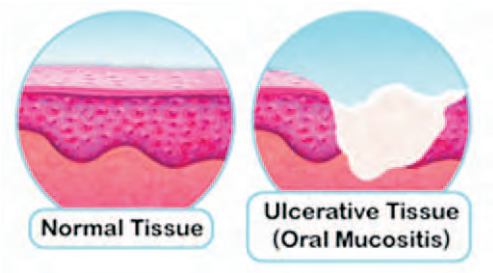
Clinical Significance: Natural honey is a product with rich nutritional qualities that could be a pleasant, simple, and economic modality for the management of radiation mucositis.

Keywords: Mucositis, honey, cancer, radiotherapy, Oral Mucositis Assessing Scale, OMAS

Citation: Motallebnejad M, Akram S, Moghadamnia A, Moulana Z, Omidi S. The Effect of Topical Application of Pure Honey on Radiation-induced Mucositis: A Randomized Clinical Trial. J Contemp Dent Pract 2008 March; (9)3:040-047.

Introduction

Cancer is one of the major threats to public health in the developed world and increasingly in the developing countries. In developed countries cancer is the second most common cause of death.[1] When deaths are aggregated by age, cancer has surpassed heart disease as the leading cause of death for persons younger than 85 since 1999.[2] According to the *World Health Report 2004* cancer accounted for 7.1 million deaths in 2003, and it is estimated the overall number of new cases will rise by 50% in the next 20 years.[3] Oropharyngeal cancer is more common in developing countries.[4,5]



Radiotherapy plays an important role in the management of head and neck cancer. The majority of new cases with invasive head and neck cancer will require radiotherapy as a primary treatment, as an adjunct to surgery, in combination with chemotherapy, or as palliation.[6] Most patients with head and neck carcinomas, treated with curative intent, receive a dose between 50 and 70 Gy. This dose is usually given in 2 Gy fractions once a day for five days a week over a five to seven week period. In addition to an anti-tumor effect, ionizing radiation causes damage to normal tissues located in the radiation portals. The most common acute complication of radiotherapy in the head and neck region is oral mucositis.[7] Radiation mucositis is considered to be an inevitable but transient side effect of therapeutic head and neck irradiation and is strongly related to radiation dose, fraction size, volume of irradiated tissue, fractionation scheme, and the type of ionizing irradiation.[8] At present, mucositis is recognized as an epithelial and subepithelial injury that develops in five phases:[9]

1. Initiation
2. Primary damage response
3. Signal amplification
4. Ulceration
5. Healing

The Consensus Development Panel of the National Institutes of Health[10] has stated no drugs can prevent mucositis, an opinion that still holds true to date.[8,11,12] Consequently, prevention of mucositis is still limited to reduction of its severity by oral care programs, relief of pain and discomfort, and/or strategies to eliminate microorganisms that are thought to be involved in the development or promotion of radiation mucositis.[6]

Honey is a by-product of flower nectar and the upper aero-digestive tract of the honeybee, which is concentrated through a dehydration process inside the bee hive. Though honey is an age-old remedy from the time of Egyptian civilization, very recently it has found a place in modern medicine.[13] Because of its high viscosity, acidic PH, hydrogen peroxide, high osmolarity, and rich nutritional properties honey can inhibit bacterial growth and enhance healing.[14-16] Also, honey has been used to manage burns, oral infections, surgical wounds, and pressure wounds.[15-19] Biswall[13] used topical honey to manage radiation mucositis successfully for the first time.

The aim of this study is to evaluate the effect of topical pure honey on radiation mucositis.

Methods and Materials

This double blind randomized clinical trial was conducted in the Babolsar Center for Cancer from March, 2003 to August, 2004. Forty patients (18 females and 22 males with a mean age of 57.05±9.43 and 56.95±14.5, respectively) with head and neck cancer who underwent radiotherapy of the head and neck were selected. Informed consent was obtained from all participants. This project was approved by the Ethics Committee of the Babol University of Medical Sciences. Selected patients had no history of previous radio chemotherapy or other systemic diseases. All patients' blood sugar levels were checked, and those with a FBS > 150 mg/dl were not selected. All patients were advised to avoid alcohol, spicy and acidic foods, smoking, and to maintain good oral hygiene during the course of radiotherapy.

Radiotherapy was administered using Cobalt 60 at a dose of 1.8 to 2 Gy per day, five times a week up to total dose of 50 to 60 Gy (in five to six weeks).

Patients were divided into two groups. The study group of 20 patients took 20 ml pure natural honey 15 minutes before then 20 ml doses again at 15 minutes and six hours after radiotherapy. They were instructed to rinse the honey around in their mouths and swallow gradually in order to coat the oral and pharyngeal mucosa. Finding an appropriate and similar material to use as a placebo was impossible because all materials similar to honey may have some effects on mucositis because of the high viscosity or high carbohydrate concentration. As a result, the 20 patients in the control group were advised to rinse their mouths with 20 ml of normal saline (0.09%) before and after each radiotherapy session. The patients in this control group were matched to the study group by sex, age, the localization of the primary tumor, radiation dose, and general health status.

Both groups were provided instruction on adequate fluid intake, supplementation with a high protein diet, and oro-dental care. The weight of patients was measured at the beginning and at the end of treatment. During the course of treatment, patients with a severe burning sensation in the mouth, pain, or with a WBC count less than 3000/mm^3 were excluded from the study.

Examinations of the oral mucosa were performed on all patients at the beginning of treatment and continued weekly up to the end of radiotherapy by an evaluator who was blinded to the group assignments of the participants. The Oral Mucositis Assessing Scale (OMAS) was used to score the ulceration or pseudo membranous areas from 0 to 3 and erythema with scores ranging from 0 to 2 in nine distinct areas of the mouth.[11] A score of '0' is without erythema or ulceration (pseudo membranous area), and a score of 3 is an ulceration more than 3 cm in diameter or severe erythema. The final score could range from 0 to 45.

In this study pure natural honey from Thymus and Astragale in the Alborz mountains in northern Iran was used. The organoleptic, microbial, and physicochemical analysis of the honey sample was evaluated by authorized Drug and Food Control Laboratory of the Ministry of Health of Iran. A microbiological assay was done against pathogenic organisms at pure, 1:2, 1:4, and 1:8 dilutions, respectively. Cultures of *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Escherichia coli* were plated on BHI agar and a filter disc was placed on the medium. A volume of 30 μl of pure and 1:2, 1:4, and 1:8 diluted honey was placed on the

discs. In another plate 100 μl of pure and 1:2, 1:4, and 1:8 diluted honey was placed in the wells. The plates were incubated for 24 hours at 37°C and the inhibition zone was measured.

The weights of all patients were checked before and after the radiotherapy courses. Data were analyzed using the Independent Sample t-test and the Mann-Whitney and Friedman tests by means of SPSS software (SPSS Inc., Chicago, IL, USA) with $p<0.05$ considered significant.

Results

The study was completed in August 2004, and all cases received radiotherapy as planned. The distribution of primary tumors was as follows:

- Nasopharynx (20 cases)
- Oral cavity (10 cases)
- Salivary glands (3 cases)
- Hypopharynx (4 cases)
- Tonsils (3 cases)

The pH of the honey was 3.3 and its density was 1.202 g/ml. The organoleptic properties and microbial tests were compatible with standard criteria. The fructose/glucose ratio was 0.7. Antibacterial activity was negative in each dilution for all four organisms.

The 40 patients evaluated were 18 females and 22 males with a mean age of 57.05±9.43 and 56.95±14.5, respectively. In the control group three patients in the fourth week and three patients in the fifth week took medication because of severe mucositis. In addition, two patients in the fourth week and one in the fifth week of radiotherapy temporarily refused to continue the treatment.

In the study group four patients (20%) showed no evidence of mucositis during the radiotherapy course leading to refusal of treatment or taking of medication.

The mean rank of OMAS at the end of each week in two groups was estimated (Table 1).

The mucositis score of OMAS at the end of each week in the study group was significantly lower than the control group (Mann-Whitney test) ($p=0.000$) (Figure1).

The mucositis score changes for the two groups during the six weeks were compared using the Friedman test and showed significant differences in the OMAS during the six weeks ($p=0.000$) (Figure 2).

Weight loss was measured in both groups. In the study group the mean weight loss was 1±0.35 (0 to 7 kg). Ten patients showed no weight loss in this group. In the control group the mean weight loss was 6.3±0.53 (2 to 11 kg). The mean weight loss in both groups was analyzed using the independent Sample t-test which was significantly higher in the control group ($p=0.000$).

Discussion

This study showed honey had a remarkable effect on radiation mucositis which confirms the Biswal's study of the effect of honey on radiation mucositis.[13]

Radiation mucositis develops early during radiotherapy. The acute mucositis response to radiotherapy is a result of mitotic death of epithelial cells, since the cell cycle time of the

Table 1. Mean rank (95% Confidence Interval) of OMAS at the end of each week during radiation therapy in the two groups.

Weeks (OMAS)	End of Week #1 (95% CI)	End of Week #2 (95% CI)	End of Week #3 (95% CI)	End of Week #4 (95% CI)	End of Week #5 (95% CI)	End of Week #6 (95% CI)
Control	27.80 (0.2-3.35)	28.25 (3.4-9.26)	28.76 (7.19-16.58)	26.73 (8.95-18.6)	25.73 (10.35-17.64)	20.00 (11.23-17.43)
Case	13.20 (0.15-0.41)	12.75 (0.87-3.12)	11.68 (1.48-4.25)	11.45 (1.19-3.73)	10.65 (1.08-3.31)	8.00 (0.79-2.4)

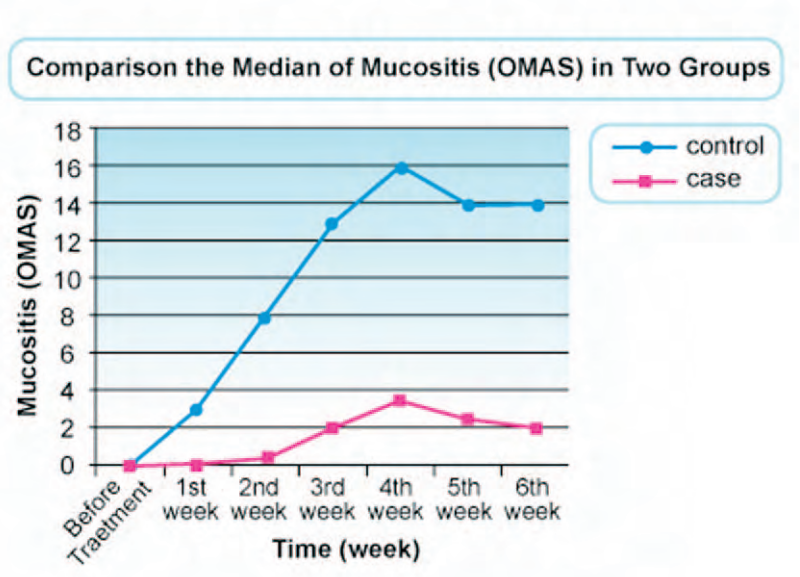


Figure 1. Comparison of the median of mucositis (OMAS) in two groups.

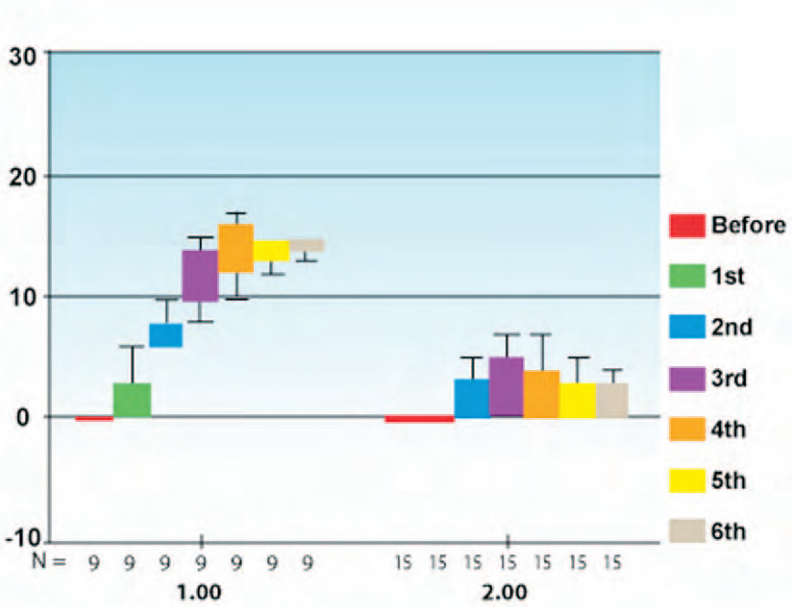


Figure 2. Mucositis changes (OMAS) during six weeks of treatment in two groups.

basal keratinocytes is about four days.[8] Radiation mucositis is defined as a reactive inflammation of the mucous membrane during radiotherapy. It is characterized by atrophy of squamous epithelial tissue, absence of vascular damage, and an inflammatory infiltrate concentrated at the basement region.[20] The early radiation reaction causes discomfort as well as difficulties in drinking, eating, swallowing, and speech, which gives rise to nutritional problems. Bacterial colonization in the oral mucosa can aggravate the mucositis and endotoxins released from gram-negative *bacilli* are potent mediators of the inflammatory process in the oral cavity.[21,22]

A major difficulty to interventional and epidemiologic mucositis research has been the lack of an acceptable, validated, and objective scoring system for mucositis. Many researchers have developed different scoring systems, often with different objectives. These systems have attempted either to eliminate subjective findings

completely or to evaluate them independent of objective findings and then integrate them into a comprehensive score. The OMAS was first suggested by Sonis[11] who showed the scale was easy to use and had a high interobserver reproducibility. The OMAS was responsive over time and measured those elements deemed to be associated with mucositis. It also showed the use of concomitant symptomatic measurements by VAS and questionnaires are likely unnecessary.[11] Because of these findings the OMAS was used for scoring of radiation mucositis in the present study.

Prevention of mucositis is still limited to reduction of its severity by oral care programs, relief of pain and discomfort, and/or choosing strategies to eliminate microorganisms that are thought to be involved in the development or promotion of radiation mucositis. Currently, most oral care programs target the following:[8]

- Removal of mucosal irritation factors
- Cleansing of the oral mucosa
- Maintaining moisture of the lips and the oral cavity
- Relief of mucosal pain and inflammation
- Prevention or treatment of infection

There are many different modalities for management of mucositis such as using transforming growth factor ß3,[23] keratinocyte growth factor,[24] chemical protection of mucosa such as amifostine,[25] G-CSF,[26] anti inflammatory agents,[27] and local antibiotic lozenges.[28] These treatments are not easy to use and produce inconsistent results.

Honey is flower nectar which is transformed and concentrated within the upper digestive tract and secreted by honey bees. Honey contains moisture, fructose, glucose, sucrose, maltase and other compounds, along with trace elements.[29] The quality of honey basically depends upon its source and dilution. In the present study honey obtained mainly from Thymus and Astragale in northern Iran was used.

In the recent past honey has been used for the treatment of burn wounds,[16] infected surgical wounds,[18] pressure ulcers,[19] and postoperative wound infections.[30,31] Important factors which influence the effectiveness of honey are as follows:[13]

- Its hygroscopic properties
- Its acidic pH
- The conversion of hydrogen peroxide from glucose oxydase and gluconic acid
- Its enzymes and tissue nutrition minerals and vitamins that help repair tissue directly

The antibacterial effects of honey are divided into physical and chemical effects. The physical effect is based on high osmotic properties so it can extract water from bacterial cells and cause them to die.[14] The chemical effect of honey is related to elements having antibacterial properties such as the glucose oxidase enzyme which produces hydrogen peroxide and prorolis.[14,17]

The effect of honey on infection is not only related to antibacterial agents but also to its effect on the proliferation of B and T lymphocytes.[32] Furthermore, 1% honey in a tissue culture can release TNF, IL-1, and IL-6 from monocytes.[33]

The comparison of the results of the present study to the Biswall[13] study shows the effect of honey on mucositis is not only due to its antibacterial properties since the honey used had no effect against the same microorganisms studied by Biswall. However, the honey used in the present study had a similar effect on radiation-induced mucositis.

Conclusion

Within the limits of the Biswall and present study, it seems the effect of honey is not only based on antibacterial effects or geographic location and source of pollens but due to the combination of all useful properties in natural honey. However, further studies are needed to confirm these results.

Clinical Significance

Natural honey is a product with rich nutritional qualities that could be a pleasant, simple, and economic modality for the management of radiation mucositis.

References

1. Petersen PE. Strengthening the prevention of oral cancer the WHO perspective. Community Dent Oral Epidemiol. 2005; 33:397-9.
2. Jemal A, Murrey T, Ward E, Samuel A, Towari RC, Ghafoor A, Feuer EJ, Thun MJ. Cancer statistics 2005. CA Cancer J Clin. 2005; 55(1):10-30.
3. World Health Organization & International Union against Cancer. Global action against cancer. Geneva: WHO, 2003.
4. Stewart BW, Kleihues P. World Cancer Report, 1st ed. International Agency for research on cancer, Lyon WHO 2003.
5. Petersen PE. The World Oral Health Report 2003: continuous improvement of oral health in the 21st century- the approach of WHO Global Oral Health Programme. Community Dent Oral Epidemiol 2003; 31(supp.1):3-24.
6. Scully C, Epstein JB. Oral health care for the cancer patient. Oral Oncol Eur J Cancer 1996; 32 B:281-292.
7. Vissink A, Jansma J, Spijkervet FKL, Burlage FR, Coppes RP. Oral sequellae of head and neck radiotherapy. Crit Rev Oral Biol Med. 2003; 14(3):199-212.
8. Vissink A, Burlage FR, Spijkervet FKL, Jansmal J, Coppes RP. Prevention & treatment of the consequences of head and neck radiotherapy. Crit Rev Oral Biol Med. 2003; 14(3):213-225.
9. Sonis ST. The pathophysiology of mucositis. Nature Reviews Cancer. 2004; 4: 277-84.
10. Consensus statement. Oral complications of cancer therapies. NCI Monogr. 1990; 9:3-8.
11. Sonis ST, Eilers JP, Epstein JB, Le Vaque FG, Liggett WH, Mulagha MT, Peterson DE, Rose AH, Schubert MM, Spijkervet FK, Wittes JP. Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Cancer. 1999; 85:2103-211.
12. Sutherland SE, Brownman GP. Prophylaxis of oral mucositis irradiated head and neck cancer patients: a proposed classification scheme of interventions & Meta analysis of randomized controlled trials. Int J Radiol Oncol Biol Phys.2001; 49:917-930.
13. Biswall MM, Zakaria A, Ahmad NM. Topical application of honey in the management of radiation mucositis: Apreliminary study. Support Care Cancer. 2003; 11:242-248.
14. Liza G, Ovington LG. Honey: Ancient cure or modern alternative? Wound Care newsletter. 1999 Jan;4:1-3.
15. Molan PC. The theory of honey in the management of wound. J Wound Care. 1999; 8(8):423-6.
16. Subrahmanyam M. A prospective randomised clinical and histological study of superficial burn wound healing with honey and silver sulfadiazine. Burns. 1998; 24(2):157-61.
17. Molan PC. The potential of honey promote oral wellness: Gen Dent. 2001; 49(6):584-9.
18. Cooper RA, Molan PC. The use of honey in healing a recalcitrant wound following surgical treatment of hidradentitis supportive. Eur J Clin Microbiol Inf Dis. 2001; 20:758-759.
19. Vander Weyden EA. The use of honey for the treatment of two patients with pressure ulcers. Community Nurs. 2003; 8(12):514-20.
20. Handschel J, Prott FJ, Sunderkötter C, Metze D, Meyer U, Joos U. Irradiation induces increase of adhesion molecules and accumulation of 2-integrin-expressing cell in humans. Int J Radiat Oncol Biol Phys.1999; 45:475-481.
21. Al-Tikriti U, Martin MV, Bramley PA. A pilot study of the clinical effects of irradiation on the oral tissues. Br J Oral Maxillofac Surg. 1984; 22:77-86.
22. Bernhoft CH, Skaug N. Oral findings in irradiated edentulous patients. Int J Oral Surg.1985; 14:416.
23. Wymenga AN, van der Graaf WT, Hofstra LS, Spijkervet FK, Timens W, Timmer-Bosscha H, Sluiter WJ, van Buuren AH, Mulder NH, de Vries EG. Phase I study of transforming growth factor ß3 mouthwash for prevention of chemotherapy induced mucositis. Clin Cancer Res.1999; 5(6):1363-1368.
24. Dorr W, Noack R, Spekl K, Forrell CL. Modification of oral mucositis by keratinocyte growth factor: single radiation exposure. Int Radiat Biol. 2001; 77:341-347.
25. Schonekas KG, Wagner W, Prott FJ. Amifostine a radioprotector in locally advanced head and neck tumors. Strahlenther Onko.1999; I 175 [Suppl 4]:30-33.

26. Mascarin M, Franchin G, Minatel E, Gobitti C, Talamini R, De Maria D, Trovò MG., The effect of granulocyte colony-stimulating factor on oral mucositis in head and neck cancer patients treated with hyperfractionated radiotherapy. Oral Oncol.1999; 35: 203-8.
27. Epstein JB, Stevenson-Moore P, Jackson S, Mohamed JH, Spinelli JJ. Prevention of oral mucositis in radiation therapy: a controlled study with Benzydamine hydrochloride rinse. Int J Radiat Oncol Biol Phys. 1989; 16:1571-5.
28. Okuno SI, Foote RL, Loprinzi CL, Gulavita S, Sloan JA, Earle J, Novotny PJ, Burk M, Frank AR. A randomized trail of a nonabsorbable antibiotic lozenge given to alleviate radiation-induced mucositis. Cancer.1997; 79(11):2193-9.
29. Qiu PY, Ding HB, Tang YK, Xu RJ. Determination of chemical composition of commercial honey by near-infrared spectroscopy. J Argic Food Chem.1999; 47:2760-2765.
30. Vardi A, Barzilay Z, Linder N, Cohen HA, Paret G, Barzilai A. Local application of honey for treatment of neonated postoperative wound infection. Acta Paediatr.1998; 87(4): 429-32.
31. Al-Waili NS, Saloom KY. Effect of topical honey on post-operative wound infections due to gram positive and gram negative bacteria following caesarean sections and hysterectomies. Eur J Med Res.1999; 4(3):126-30.
32. Abuharfeil N, Al Oran R, Abo-Shehada M. The effect of bee honey on the proliferative activity of phagocytes. Food Argic Immunol. 1999; 11:169-77.
33. Tonks AJ, Cooper RA, Jones KP, Blair S, Parton J, Tonks A. Honey stimulates inflammatory cytokine production from monocyte. Cytokine. 2003 Mar 7; 21(5):242-7.

About the Authors

M. Motallebnejad, DDS, MS

Dr. Motallebnejad is an Assistant Professor in the Department of Oral Medicine of the Faculty of Dentistry at the Babol University of Medical Sciences in Babol, Iran. In 1991 she received her dental degree from Tehran University of Medical Sciences in Tehran, Iran and her Masters degree in Oral Medicine from the same University in 1997.

e-mail: mmotallebnejad@yahoo.com

S. Akram, MD

Dr. Akram is an Assistant Professor in the Department of Oncology at Babol University of Medical Sciences in Babol, Iran. She received her MBBS degree from the MR Medical College in Gulbarga, Karnataka, India in 1987 and her medical degree in Radiotherapy-Oncology in 1993 from the Post Graduate Institute of Medical Education and Research (PGIMER) in Chandigarh, India.

A. Moghadamnia, PhD

Dr. Moghadamnia is a Professor in the Department of Pharmacology at Babol University of Medical Science in Babol, Iran. He received his undergraduate education at Tehran University of Medical Sciences (1994) in Tehran, Iran. In 2003 Dr. Moghadamnia received his Doctorate in Clinical Pharmacokinetics from Sheffield University in Sheffield, UK.

e-mail: moghadamnia@yahoo.com

Z. Moulana, MSc

Ms. Molana is a microbiologist in the Department of Microbiology and a member of the Paramedical Faculty in the Department of Laboratory and Environmental Health at the Babol University of Medical Science in Babol, Iran.

S. Omidi, DDS

Dr. Omidi is a general dentist in private practice. She received her dental degree in 2005 from Babol University of Medical Sciences in Babol, Iran.

Aknowledgement

The authors would like to express their appreciation to Mr. Hadjian and all the staff of Shahid Rejaie Center of Radiotherapy in Babolsar, Iran for their assistance with this study.

This project was supported by the Research Council of Babol University of Medical Sciences.

We also appreciate Dr. Sabetha for useful advices.