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The Effectiveness of Local Application of Aqueous Cream and Amorphous Hydrogel on the Radiated Skin as a Measure to Prevent Skin Reactions in Patients with Nasopharyngeal Cancer who are Undergoing Radiotherapy
Abstract of dissertation entitled:

The effectiveness of local application of aqueous cream and amorphous hydrogel on the radiated skin as a measure to prevent skin reactions in patients with nasopharyngeal cancer who are undergoing radiotherapy

submitted by Yu Sau Ling

for the degree of MSc in Health Care (Nursing)

at The Hong Kong Polytechnic University in November 05

Abstract

Radiotherapy skin reactions occur commonly in clinical practice and cause number of problems for patients and their carers.

Purpose / aim: The purpose of this study was to determine whether the application of aqueous cream and amorphous hydrogel would decrease the incidence of skin reactions including erythema, dry desquamation, and confluent desquamation; toxicity of pain and itchy in patients with nasopharyngeal carcinoma (NPC) undergoing radiotherapy.

Design: Quasi-experimental clinical trial study.

Setting: Radiotherapy centre in a private hospital.
Sample: 40 patients with nasopharyngeal carcinoma, who required a full course of radiotherapy using intensity-modulated radiation therapy (IMRT).

Intervention: Prophylactic skin care began on the first day of radiotherapy and continue daily (including non-treatment days) until four weeks after the end of treatment. Patients were assigned to the experimental group using aqueous cream with amorphous hydrogel. Patients were instructed to apply aqueous cream and amorphous hydrogel to the area at various intervals throughout the course of treatment. Aqueous cream was used on the first two weeks and the last two weeks. On week three and four, aqueous cream and amorphous hydrogel were used twice a day alternately. From fifth week onwards till the ninth week, only hydrogel was used four times a day.

Results: Aqueous cream and hydrogel was significantly better effective in reducing the incidence of skin reaction including erythema (P = 0.00^a), dry desquamation (P = 0.003^a) and itchy toxicity (P = 0.004^a), but they did not significantly reduce confluent desquamation (P = 0.133^a) and radiation-induced skin pain (P = 0.93^a). (^a, Log Rank test)

Conclusion: Although the sample size was small, there is a place for cream and hydrogel as a prophylactic skin care in the prevention of radiation-induced skin reactions.
Acknowledgements

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The author thanks the HKSH department of radiotherapy’s doctor Teo Man Lung, Peter who supported the author to do this study.

The author also thanks the nursing staff at the HKSH department of radiotherapy, who assisted in the coordination and performance of skin assessments for the study, in addition to continuing to do their regular nursing duties, and the nursing Director, Ms Manbo Man for her encouragement and support.

The author thanks from the bottom of heart to the academic supervisor and co-supervisor Professor Samantha Pang and Tony Chan for the guidance of the study.
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Introduction:

Nasopharyngeal carcinoma (NPC) is endemic in southern China and Southeast Asia. Radiotherapy is the standard treatment for NPC (Sham, Kwong, & Chua, 2003).

Though the technologies and techniques for administering radiotherapy have been improved since its inception, adverse effects on skin integrity continue to be a problem for those patients who receive radiotherapy. About 90 - 95% of patients have been reported that they have experienced some degree of reaction during radiotherapy (De Conno, Ventafridda & Saita, 1991; Porock & Kristjanson, 1999). Many patients suffer from radiation-induced skin reactions, which develop around two to three weeks after starting radiotherapy treatment, and may persist for up to 4 weeks after the treatment has finished (Blackmar, 1997). Erythema, dry desquamation and confluent desquamation (figure 1) are the most commonly skin reactions. This is especially true for the NPC patients, as they have to undergo 7-week course of 7000centiGy or 70Gy radiation treatment. The treatment for each section is approximately 35 minutes (Huang et al., 2000). Therefore, skin reactions are a primary nursing concern in caring for the patients undergoing radiotherapy (Lawton & Twoomey, 1991; Sitton 1992; Barkham, 1993). Thus, this paper is going to study the effectiveness of local application of Aqueous Cream and amorphous hydrogel on the radiated skin as a measure to prevent skin reaction in patients with nasopharyngeal cancer who are undergoing radiotherapy.

Figure 1: Confluent desquamation
Radiation and skin:

Under normal conditions, the surface of the skin is in a constant state of renewal. Cells in the epidermis, or outermost layer, shed continuously and are replaced by cells (keratinocytes) that have been formed by mitosis in the basal later of the epidermis. (After mitosis, one keratinocyte remains in the basal layer, while the other moves to the skin surface). The keratinocyte on the surface then flattens, dehydrates, becomes keratinized, and eventually sheds. The average turnover time of the entire process is about four to six weeks (Bomford et al, 1993).

The underlying cause of radiation damage to skin is the ionization of atoms and molecules of the chromosomal DNA within the cells of the epidermis. The basal layer is particularly sensitive and damage to these cells can produce a wide spectrum of reactions. Different types of radiation have different tissue absorption profiles and therefore different effects on the skin (Parker & Juillard, 1988). Shorter wavelength radiation such as electron beams result in the skin receiving 80% of the dose, consequently exhibiting a greater reaction, while the megavoltage machines, now currently used, render only 20 – 30% of the total dose to the skin, displaying less reaction (Duchesne & Horwich, 1992).

The usual recommended radiation dose for NPC is 70 Gy with conventional fractionation (2 Gy per fraction, 5 fractions per week over 7 weeks) and extra 60-65Gy for carcinoma secondary to neck nodes. For prophylactic neck irradiation, 50-60 Gy is usually recommended. As the radiation dosage is high almost all the NPC patients would develop radiation-induced moist desquamation on both side of the neck (Huang et al., 2000; Mak et al 2000). It is because the ionizing radiation kills the cells of the skin’s basal layer (figure 2).
Levels of skin reactions:

Adverse skin effects range from minimal erythema to moist desquamation. Within 24 hours after the first radiation dose, a small percentage of patients may experience erythema of the skin; however, this is an exception rather than the norm. A patient usually does not experience a skin reaction until receiving an accumulated dose of 2000 cGrays (20Gy) (Korinko & Yurick, 1997).

When erythema - a drying and reddening of the skin - occurs it may appear in waves, so it may disappear during days without treatment and then reappear after the next treatment dose. Erythema usually appears during the second or third week of radiotherapy and lasts from between 20 and 30 days. It is caused by the release of histamine-like substances from damaged germinal cells which in turn causes dermal oedema, purities, erythrocyte extravasations and dilatation of the capillaries which is exhibited as various shades of skin redness (Walker, 1982; Blackmar, 1997).

Radiation also stimulates melanocytes, which are contained in the epidermis. These melanin-producing cells give skin its colour and protect the body from ultraviolet light. When they are stimulated, increased pigmentation occurs, giving the
affected area a tanned appearance, skin appendages-hair, sebaceous glands, and sweat glands-in the treatment field are also affected by the therapy (Korinko & Yurick, 1997).

Approximately about two to three weeks after the commencement of radiation therapy, the skin surface cells injured at the beginning of treatment shed at a faster rate than normal. If the surviving basal cells are dividing fast enough that new cells are available to replace the dead ones, the skin surface remains dry and the patient may experience dry desquamation-dry, flaking skin and pruritus. Dryness is also due to the decreased functioning of sweat glands (Dini et al, 1993). At the stage of dry desquamation, patients experience pain as skin dryness activate nerve fibers causing pain (Campbell, 1996).

However, if new cell proliferation is inadequate or does not occur, and if the basal layer has not recovered, moist desquamation with exposed dermis and oozing of serum occurs (Sitton, 1992). At this stage radiotherapy is usually temporarily stopped (Marks, 1987).

If the radiotherapy continues at a time when moist desquamation is evident, extensive skin and subcutaneous necrosis may occur (Souhami & Tobias, 1995). Necrosis is a combination of ischaemia due to acute vascular occlusion and cell death due to terminal nuclear destruction. (Hilderley, 1997).

The variation in the severity of skin reaction experienced by individuals is often raised on several variables or factors. The factors are usually listed as: radiation
dose, time period over which the dose is administered, size of field (volume) and chemotherapy administration (McDonald, 1992; Sitton, 1992).
Current guidelines for skin care during radiotherapy:

The aim of skin care guidelines is to maintain the stratum corneum intact for as long as possible. This is achieved by reducing undue irritation or trauma to the irradiated skin.

Radiation only affects the skin within the treatment field; therefore, skin guidelines only apply to that specific area. According to Sitton (1992) and Korinko and Yurick (1997), general skin care guidelines include the following:

- Restriction of soaps, deodorants, or perfumes in the treated area is usually suggested.
- Soft, loose cotton clothing is also recommended, as is protecting the area from the elements and extremes of temperature.
- Also, topical agents that contain metals are contraindicated as they accumulate the dose of radiation at the skin level.

The radiotherapy departments of Hong Kong also carry out these guidelines for skin care during radiotherapy. However, most NPC patients undergo radiotherapy suffering from radiotherapy-induced moist desquamation (Mak et al., 2000).
Topical skin care products use in radiotherapy:

As a prophylactic measure, Korinko and Yurick (1997) suggested that before the first treatment, patients should moisturize the treated area with a hydrophilic lubricant—one that absorbs water—such as Aqueous Cream, or aloe-vera gel. When dry desquamation occurs, the skin should be moisturized at least four times a day.

Several papers have been published as educational resources for nurses to assist patients in making clinical decisions about topical treatment of radiation skin reactions. These papers suggested the use of light creams, ointments, and steroids to moisturize the skin when erythema or dry desquamation occurs. (Barkham, 1993; Blackmar, 1997; Porock & Kristjanson, 1999). However, there is a paucity of empirical evidence to support the use of creams to prevent the development of radiation skin reactions or promote healing.

Aqueous cream is a simple water-based moisturizing cream. Creams are emulsions of oil in water, water washable, and completely absorbed into the skin (Sitton, 1992). It could increase skin pliability and flexibility (Campbell, 1996). Boot-Vickers and Eaton (1999, p.707) asserted that the use of aqueous cream to prevent the development of dry desquamation.

The management of moist desquamation appears to be based on the principle of moist wound healing with the most highly recommended products being dressings that promote a moist wound environment (Margolin et al., 1990). The use of hydrogels, in both sheet and gel (amorphous) form, is also recommended for moist desquamation (Boot-Vickers & Eaton 1999, Zimmerman 1998, Korinko & Yurick
managing reactions in skin folds such as supraclavicular area or the perineum (Boot-Vickers & Eaton 1999). Hydrogel was effective in reducing discomfort and speeding healing of moist desquamative reactions (Pickering & Warland, 1992). Crane (1993, p.98) reported that hydrogel had a soothing and cooling effect and could prevented skin break down.

As there were different topical skin care product recommendations, skin care products were recommended vary from among radiation department and physicians as determined by Barkham (1993, p.735) in a survey undertaken to determine the prevalence of skin reactions and the treatments used in various centres. Relatively few scientifically designed studies have been conducted comparing the efficacy of prophylactic skin products.

Clinical Studies on Radiation-Induced Skin Reactions:
Hydrating the skin as a prophylactic measure by means of different kinds of topical agents to prevent radiation-induced skin reactions has been recommended frequently in the literature (Sitton 1992; Hilderley 1997; Korinko & Yurick 1997) but is not often done by Flemish radiotherapy nurses (D’Haese et al. 2005).

Heggie et al. (2002) conducted a randomized controlled trial study of 208 patients on the efficacy of topical aloe vera gel on irradiated breast tissue. The study concluded that aqueous cream was superior to aloe vera gel in reducing the acute radiation skin side effects of dry desquamation and pain. A 98% aloe vera gel might reduce erythema. The author suggested that topical aloe vera gel might be beneficial in conjunction with aqueous cream for use on breast tissue undergoing irradiation. However, 98% aloe vera gel is not in use in Hong Kong radiotherapy departments. Amorphous hydrogel is more commonly used in the study department in treating radiotherapy-induced skin breakdown.

Another study conducted by Olsen et al. (2001) was a comparison between washing with soap and applying aloe vera with washing with soap only. They found that when the cumulative dose increased over time there was a protective effect of using aloe vera (P = 0.001). Aloe vera delayed the onset of skin problems.

Williams et al. (1996) conducted two randomised trials in which they compared aloe vera gel and a placebo gel (n = 194) with aloe vera gel and no treatment (n = 108) on irradiated breast tissue and chest wall. They found that there was a contradiction with Olsen et al (2001). There was no differences in skin reactions and concluded that aloe vera did not protect the skin against radiation-induced injury.
A randomized controlled trial of sucralfate cream versus a placebo for 50 breast cancer patients (Maiche et al. 1994). Unfortunately, no details were reported on the reliability of skin reaction measures. Results showed that early erythema appeared later and recovery was faster in the area treated with sucralfate cream. This study provides convincing evidence of the benefits of sucralfate cream. Sucralfate cream is not in use in the study department.

Witt et al. (1991) subjected their commonly used product, Natural Care Gel, to a small pilot study of 32 breast cancer patients and found that it did have clinically important benefits for their patients as they had less purities, improved skin texture and increase skin and nipple comfort. This study did not state their skin assessment tool.
**Importance of current study:**

Radiation-induced skin reactions occur commonly in clinical practice and cause number of problems for patients and their carers. Hydrating the skin seems to have a positive effect on healing time (Naylor *et al.* 2001). However, there is little clinical evidence upon which to base the choice of prophylactic topical agents to prevent radiation skin reactions. As a result, the skin care might vary considerably between hospitals and practitioners (Campbell 1996; Blackmar 1997).

As Blackmar mentioned (1997, p.173) patients suffering from acute radiation-induced skin reactions that is developed after around two to three weeks of radiotherapy treatment and might persist for up to four weeks after the treatment had finished. The aim of applying Aqueous cream and amorphous gel from the first day of radiation treatment till four weeks after finishing treatment was to hydrate the skin and provide a better environment for the basal cell to take mitosis.

In Hong Kong skin care guidelines given to patients usually entail a change in hygiene routine, restrictions in clothing and, in some cases, restriction on activities such as swimming. The rationale behind these guidelines is to prevent exacerbation of the inevitable radiation-induced skin reaction rather than to prevent the development of skin reactions (Porock & Kristjanson 1999). Prophylactic skin care products are not allowed to use as a moisturizer for the patients who undergo the treatment of radiotherapy. Studies on the effectiveness of the topical products as a prophylactic skin care products as a measure for prevention of radiation-induced skin reaction in Chinese is rare. And also, studies on the topical products as a prophylactic skin care products as a measure for prevention of radiation-induced skin reaction for the nasopharyngeal carcinoma is not common. As taking into account all the evidence
from the reviewed articles it is possible to develop some preliminary guidelines for the prevention of acute radiation induced skin reactions. These will of course need to be applied to practice and their clinical performance fully evaluated through audit and clinical review.
Aim of the Study:

The aim of the study was to test the effectiveness of local application of aqueous cream and amorphous hydrogel on the radiated skin as a measure to prevent skin reaction for the patients with nasopharyngeal cancer who was undergoing radiotherapy.

The hypotheses was developed, the use of aqueous cream and hydrogel would decrease the incidence of skin changes for the NPC patients who were undergoing radiotherapy by looking at the effects of:

- The time for the skin to become stage 1 condition (erythema),
- Skin condition at each assessment.
- Time required for the healing of radiotherapy-induced skin problems,
- Patients’ rating of pain frequency and pain severity.
- Patients’ ratings of itch.
Methodology

Study design -

Because of the practical reason, the study was used a quasi-experimental design. Only one doctor who supported the author to do the study. The other doctors refused their patients to apply cream or gel. Therefore subjects were not randomly allocation. The study was hypothesized that the application of aqueous cream and amorphous hydrogel would be effective in prevention of skin reaction on the radiated skin for patients with nasopharyngeal cancer who were undergoing radiotherapy. Thus, all subjects under the doctor who supported the author to do the study were assigned to the intervention group, and those who were under other doctors refused their patients to apply cream or gel were assigned to the control group. Considering the study design, one should note that the two groups were very similar. They had the same treatment radiation dosage of 70Gy with or without the same concurrent chemotherapy.

The study was drawn from the radiotherapy department of a private hospital over a period of 6 months.

Sample:

The power of this study was estimated on one of the primary outcome measures, the skin reactions on itchy. The Kaplan-Meier survival analysis was employed, and used the log-rank test was used to test for differences between the two arms and a moderate hazard ratio (=0.219) was chosen for this study (Olsen et al. 2001). The required sample for each group was 120 (total=240), and this number
could achieve 80% power at a 5% level of significance (nQuery advisor 2001). However, at the end of this study, only 40 samples were recruited (control=19, and experimental=21), the power was drop to 20% only.

**Sample criteria:**

A total of 40 patients were recruited in the study. All subjects who were allowed to apply cream or gel were assigned to the intervention group, and those who were not allowed to apply cream or gel, were assigned to the control group. The sample comprised eligible adult patient who was diagnosed with nasopharyngeal carcinoma. All participants were having a standard dose of 70Gy radiotherapy using intensity-modulated radiation therapy, with or without a boost to the tumour bed. Written informed consent was required. However, concurrent chemotherapy in weeks 1, 4 and 7 as part of the treatment regimen was acceptable.

Exclusion criteria involve patients who had:

- Skin disease
- Allergy to aqueous cream or hydrogel
- Fail to comply
- Body mass index less than 18kg/m2 as malnutrition causing a delay in wound healing
- Current administration of antibiotics which cause a false negative of wound infection
- The age < 18
- The patients who were not diagnosed with nasopharyngeal carcinoma
**Intervention:**

Patients was assigned to one of two arms: (1) topical aqueous cream on the first two weeks and the last two weeks, and topical aqueous cream and amorphous hydrogel on weeks three to four, and topical amorphous hydrogel on weeks five to nine on the irradiated area, or (2) a control arm without topical agent.

The skin care regimen began on the first day of radiotherapy and continued daily (including non-treatment days) until four weeks after the end of treatment. For experimental arms, the application was used 4 times daily basing on the suggestion by Korinko and Yurick (1997, p.42).

The rationale for the experimental arm using topical aqueous cream on the first two weeks and the last two weeks, and the topical aqueous cream and amorphous hydrogel on weeks three to four on the irradiated area was: radiation-induced skin reactions developed around two to three weeks after starting radiotherapy treatment, thus, there was a shift of using aqueous cream and hydrogel twice a day alternately in stead of aqueous cream only. From fifth week onwards till the ninth week, only hydrogel was used four times a day as hydrogel had a soothing and cooling effect and could prevent skin breakdown (Crane, 1993). After the completion of radiotherapy at week ten to eleven, the application of hydrogel was shift to the use of aqueous cream as aqueous cream is more beneficial in reducing skin dryness (Heggie at el. 2002).

In addition, the research nurse gave routine skin care recommendations for patients undergoing radiotherapy. This advice included using no soap on the treatment site, and wearing loose cotton clothing next to treated area, and no need to shave.
Measures:

Demographic data:

A standard data collection form was used to gather patients' demographic data, a brief medical history, and other related information from participants such as body weight and height to calculate the body mass index (BMI), which indicated the percentage of ideal body weight (Skipper, Szeluga & Groenwald, 1993) before the patients were recruited. Garrow (1988) suggested that BMI for normal men and women should be in the range of 18 to 26kg/m². Details of radiation on the dosage and fractions, and any chemotherapy treatment were also included.

Study variables included age, sex, skin types, chemotherapy administration and the dosage of radiation. Dry skin referred to roughened, flaky or scaly skin that was less flexible than normal and dry to the touch. Follicular accentuation was offer prominent on extensor surfaces and the condition was aggravated by cold, dry climates or seasons (Siddappa, 2003). Normal skin looked consistently, plump, and vibrant. Oily skin was characterized by shiny, thick and dull coloured. Often a chronically oily skin had coarse pores and pimples and other embarrassing blemishes. All of the above data were included in data collection.

Each patient's skin was going to assess weekly by an oncology nurse throughout radiation treatment and the following four weeks after treatment. The following aspects of the skin reaction were systematically evaluated and recorded: onset of skin reaction, the grading of skin reaction that was based on the Oncology Nursing Society (ONS) Radiation Skin Reaction Scoring System (Blackmar & Bull-Hurst, 1994), duration of dry or confluent desquamation, a pain score, and an itchy
score. On completion of the study, the two arms was compared to see if a statistically significant difference in skin reaction existed between the group, with alpha set at $P = 0.05$. 
Assessment tool:

The weekly radiation-induced skin reaction assessment form was based on the Oncology Nursing Society (ONS) Radiation Skin Reaction Scoring System:

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No changes noted</td>
</tr>
<tr>
<td>1</td>
<td>Faint or dull erythema, follicular reaction</td>
</tr>
<tr>
<td>2</td>
<td>Bright erythema</td>
</tr>
<tr>
<td>3</td>
<td>Dry desquamation with or without erythema</td>
</tr>
<tr>
<td>4</td>
<td>Small to moderate wet desquamation</td>
</tr>
<tr>
<td>5</td>
<td>Confluent moist desquamation</td>
</tr>
<tr>
<td>6</td>
<td>Ulceration, hemorrhage, or necrosis</td>
</tr>
</tbody>
</table>

Radiation pain score:

Radiotherapy caused different degrees of pain for different people. Most people built up slowly over the course of radiation. Radiotherapy produced pain due to nerve irritation, swelling around treated areas and skin soreness. The radiation skin was more sensitive to touch and had a burning sensation. If skin broke down, the skin could be quite painful because of the exposure of nerve endings (Weiss, 2005). As pain was an aspect of radiation reactions that was not included on the ONS Radiation Skin reaction Scoring System. Pain was therefore measured separately using a 10 points scale where zero represented no pain and 10 represented the worst pain the patient could imagine. Participants were asked to rate the worst radiation pain they had experienced with the skin reaction during the week preceding each observation.
Itchy score:

As skin was getting dry, participants were complaint of itchy skin. A 5 points scale was used to measure patient's comfort. Zero represented no itchy whereas 5 represented the worst itchy feeling. Participants were asked to rate the worst itching toxicity on the treated area they had experienced with the skin reaction during the week preceding each observation.
Procedure:

Eligible patients were approached in the radiotherapy department and invited to participate in the study. Informed consent was obtained from the patients willing to participate.

The skin-care regimen began on the first day of radiotherapy and continue daily (including non-treatment days) until four weeks after the end of treatment. An experimental arm using aqueous cream on the first two and last two week, and aqueous cream and amorphous hydrogel on weeks three to four, and from fifth week onwards to ninth week, amorphous hydrogel only was applied four times daily on the irradiated area. Patients would be advised not to apply the skin care product two hour preceding treatment as these products could cause a more severe skin reaction (Korinko & Yurick, 1997).

In addition, the research nurse gave routine skin care recommendations for patients undergoing radiotherapy to each group. This advice includes using no soap on the treatment site, and wearing loose cotton clothing next to treated area, and did not shave. Each patient’s skin was going to assess weekly by an oncology nurse throughout radiation treatment and at four weeks after treatment as skin getting worse in two weeks time and the average turnover time of the entire epidermis is about 4 weeks (Rae, 1999). Skin scoring was conducted per the Oncology Nursing Society (ONS) Radiation Skin Reaction Scoring System. Assessments were conducted prior to the first radiotherapy treatment and weekly during regularly scheduled on-treatment visit with the oncology nurse.
The research nurse demonstrated how to apply the cream or the hydrogel to make sure that the patient did not rub the skin when applying the cream or gel. This procedure was also to test whether the patient was allergic to those topical agents. The oncology nurse recorded the weekly skin assessments that included skin reaction, pain score and itchy score, starting with a base-line assessment on day 1 of treatment. A final assessment was done at four weeks after treatment.
Data Analysis

Data were coded and entered into the computer for analysis using the Statistical package for Social Sciences. Chi-squares, Fishers’ exact, and Mann-Whitney U tests were used to compare subjects’ baseline characteristics (e.g. gender, skin type, had or had not chemotherapy, booster radiation dose) by two arms (control vs. experimental) to ensure their homogeneity. Three outcome measures (skin reaction, pain and itchy reaction) were collected at several time periods for all subjects. Groups compared severity level and frequency of reaction on each outcome as well. For each outcome at each time point, Kaplan Meier survival analysis method (Log rank test) was used to examine any differences by two arms on subjects’ occurrence day. Mann-Whitney U test was used to compare subjects’ pain and itchy scores by two arms at each time period.

Ethical Considerations:

Participation in this study should be voluntary. The patients were approached first to determine whether they were interested in the study. The research nurse gave verbal explanation about the purpose of the study and its potential contribution to the body of knowledge on radiation-induced skin reaction. Written consent obtained from the patients before their participation in the study.

All the participants were at liberty to terminate their participation. Confidentially was to be ensured. This study was approved by the Ethical Review Committee, Hong Kong Sanatorium & Hospital and Hong Kong Polytechnic University.
Results

41 subjects were recruited in the study. One subject from the control group developed an allergic skin reaction to the concurrent chemotherapy. Thus, subject was excluded from the analysis. Data from the remaining 40 subjects, 19 (47.5%) were in the control arm and 21(52.5%) were in the treatment arm, 25 males (62.5%) and 15 females (37.5%). The subjects ranged in age from 33 – 88 years. The median age was 45 years. Subjects were classified into two age groups (younger than 45 years, 45 years and older). The distribution of baseline subject characteristics by both arm were summarized in Table 1. Total treatment RT dose (cGy) for each subject was 7000. Booster dose for the neck lymph node region was dichotomized into < 6500 cGy or ≥ 6500 cGy, based on the median dose of the frequency distribution. The overall proportion of combination therapy (radiotherapy combined with chemotherapy) was 77.5% (n = 31). The control group had a higher proportion of patents receiving chemotherapy in combination with radiotherapy 54.8% (n=17) as compared with 45.2% (n = 14) in the experimental group. The subjects’ skin texture was also classified into three types: dry, normal, and oily. The chi-square test was used to test differences in proportions between the control and experimental groups regarding gender, age, whether chemotherapy or booster radiation dose was received. No significant differences were found between the two groups regarding the age (p=0.54), gender (p=0.57), skin type (p=0.55), chemotherapy (p=0.13), and boost dose (p=0.39) (Table 1). All of the subjects developed radiotherapy-induced moist desquamation had a wound on both sides of the neck.
Table 1:

Comparison of Baseline Characteristics by Control and Experimental arms

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n=40) n (%)</th>
<th>Control (n=19) n (%)</th>
<th>Experimental (n=21) n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25 (62.5)</td>
<td>11 (57.9)</td>
<td>14 (66.7)</td>
<td>0.57a</td>
</tr>
<tr>
<td>Female</td>
<td>15 (37.5)</td>
<td>8 (42.1)</td>
<td>7 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Skin type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry</td>
<td>9 (22.5)</td>
<td>3 (15.8)</td>
<td>6 (28.6)</td>
<td>0.55a</td>
</tr>
<tr>
<td>Normal</td>
<td>20 (50.0)</td>
<td>11 (57.9)</td>
<td>9 (42.8)</td>
<td></td>
</tr>
<tr>
<td>Oily</td>
<td>11 (27.5)</td>
<td>5 (26.3)</td>
<td>6 (28.6)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9 (22.5)</td>
<td>2 (10.5)</td>
<td>7 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>31 (77.5)</td>
<td>17 (89.5)</td>
<td>14 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Age, Median [Range]</td>
<td>45 [33-88]</td>
<td>46 [33-88]</td>
<td>47 [36-70]</td>
<td>0.54c</td>
</tr>
<tr>
<td>Boost (cGy) dose, Median [Range]</td>
<td>6500 [5000-6500]</td>
<td>6500 [5000-6500]</td>
<td>6500 [5000-6500]</td>
<td>0.39c</td>
</tr>
</tbody>
</table>

a, Chi-squares test; b, Fishers' exact test; c, Mann-Whitney U test.
Skin Reaction

Based on the Oncology Nursing Society (ONS) Radiation Skin Reaction Scoring System, erythema, dry desquamation, and confluent desquamation were recorded.

Erythema

Statistical significance was approached in terms of cumulative probability, prevalence, or duration for erythema toxicity. With those in the control arm experiencing a greater incidence of erythema (89.5%) than those in experimental arm (42.9%) \( (P = 0.00) \) (Table 2). The average time for the experimental arm to develop erythema was 25.9 days whereas the control arm was 18.8 days from starting radiotherapy.

Table 2:
Cumulative Probability of skin Reaction – Erythema by group comparision

<table>
<thead>
<tr>
<th>Variables:</th>
<th>Skin Change To Erythema</th>
<th>Control (n = 19) ( n (%) )</th>
<th>Experimental (n = 21) ( n (%) )</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema:</td>
<td>No</td>
<td>2 (10.5)</td>
<td>12 (57.1)</td>
<td>0.002*</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>17 (89.5)</td>
<td>9 (42.9)</td>
<td></td>
</tr>
<tr>
<td>Skin Type:</td>
<td>Normal:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1 (9.1)</td>
<td>7 (77.8)</td>
<td>0.002*</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>10 (89.9)</td>
<td>2 (22.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dry:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0 (0)</td>
<td>1 (16.7)</td>
<td>0.033*</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>3 (100)</td>
<td>5 (83.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1 (20)</td>
<td>4 (66.7)</td>
<td>0.076*</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>4 (80)</td>
<td>2 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy:</td>
<td>No</td>
<td>0 (0)</td>
<td>3 (42.9)</td>
<td>0.071*</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2 (100)</td>
<td>4 (57.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>2 (11.8)</td>
<td>9 (64.3)</td>
<td>0.001*</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>15 (88.2)</td>
<td>5 (35.7)</td>
<td></td>
</tr>
<tr>
<td>Booster RT dose:</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>----</td>
<td>-----</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6500cGy</td>
<td>0 (0)</td>
<td>3 (42.9)</td>
<td>0.07*</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (100)</td>
<td>4 (57.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 6500cGy</td>
<td>2 (13.3)</td>
<td>9 (64.3)</td>
<td>0.002*</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 (86.7)</td>
<td>5 (35.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a, Log Rank test, * significant at $P < 0.05$

With those in the control arm, subjects of normal and dry skin type experienced greater incidence of erythema on the treated area, the cumulative probability was significant ($P = 0.002$ and $P = 0.033$) respectively between the two arms. For oily skin, there was no significant difference for both arms ($P = 0.076$) (Table 2).

For subjects who had chemotherapy, those in the control arm had a significantly greater incidence of erythema (88.2%) than those in the experimental arm (35.7%) ($P = 0.001$).

Whereas subjects who had booster radiation dose $\geq 6500$ cGy, there was also significant difference between the two arms ($P = 0.002$), the experimental arm experienced smaller incidence of erythema (35.7%) than those in the control arm (64.3%).
Dry and Confluent Desquamation

The cumulative probability for dry desquamation or more skin reaction was significantly greater in the control arm (84.2%) compared with the experimental arm (42.9%) ($P = 0.003$) (Table 3) at day 35 onwards, i.e. patients had received 5000 cGy radiation dosage. The prevalence of dry desquamation in control arm was consistently greater in the control arm from day 21 after start radiotherapy (Figure 3). The average time for the experimental arm to develop dry desquamation was 44.3 days whereas the control arm was 33.2 days from starting of radiotherapy.

Figure 3:

When the subjects received 7000 cGy radiation dosage at day 49 onwards, subjects in the control arm developed confluent desquamation or more skin reaction were greater (77.9%) than the experimental arm (61.9%). However, it did not approach the statistical significance ($P = 0.133$) (Table 3). In control arm, the average
time to develop confluent desquamation was 49.1 days whereas in experimental arm was 52.3 days from starting of radiotherapy.

Table 3:

Comparison between skin change to Dry and Confluent Desquamation in Two Cumulative Dose of Radiotherapy by groups (Control, n = 19; Experimental, n = 21)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dose: 5000 cGy (at end of week 5)</th>
<th>Dose: 7000 cGy (at end of week 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes change</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>To DD</td>
<td>To DD</td>
</tr>
<tr>
<td><strong>Dry desquamation (DD):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16 (84.2)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Experimental</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 (42.9)</td>
<td>12 (57.1)</td>
</tr>
<tr>
<td><strong>Skin Type:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>9 (81.8)</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>Experimental</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (22.2)</td>
<td>7 (77.8)</td>
</tr>
<tr>
<td>Dry</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Experimental</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 (67.7)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>Oily</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4 (80)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Experimental</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (50)</td>
<td>3 (50)</td>
</tr>
<tr>
<td><strong>Chemotherapy:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Experimental</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (42.3)</td>
<td>4 (57.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>14 (82.4)</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Experimental</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 (42.2)</td>
<td>8 (57.8)</td>
</tr>
<tr>
<td>BoosterRT dose:</td>
<td></td>
<td>BoosterRT dose:</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td></td>
<td>&lt; 65Gy</td>
<td>&gt;65Gy</td>
</tr>
<tr>
<td>Control</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td></td>
<td>3 (75)</td>
<td>13 (86.7)</td>
</tr>
<tr>
<td>Experimental</td>
<td>1 (25%)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>n (%)</td>
<td>3 (42.9)</td>
<td>6 (42.9)</td>
</tr>
<tr>
<td></td>
<td>4 (57.1)</td>
<td>8 (57.1)</td>
</tr>
<tr>
<td></td>
<td>0.341</td>
<td>0.004*</td>
</tr>
<tr>
<td></td>
<td>4 (57.1)</td>
<td>12 (80)</td>
</tr>
<tr>
<td></td>
<td>3 (42.9)</td>
<td>3 (20)</td>
</tr>
<tr>
<td></td>
<td>0.96*</td>
<td>0.86a</td>
</tr>
</tbody>
</table>

a.Log Rank test, *significant at P<0.05

On day 63 or before day 63, that was two weeks after the date all the subjects finished radiotherapy, the incidence of subjects experiencing confluent desquamation changed to dry desquamation or less skin reaction was significantly greater for experimental arm (76.2%) when compared with the control arm (26.3%) (P = 0.003).

For subjects receiving 5000 cGy, those with normal and dry skin type in control arm experienced greater incidence of dry desquamation (81.8%; 100%) when compared with experimental arm (22.2%; 67.7%) respectively, the cumulative probability was significant (P = 0.008 and P = 0.03). But, subjects receiving 7000 cGy, there was no significant difference for both arms (P = 0.403 and P = 0.232). For oily skin, there was no significant difference between both arms (P = 0.258) when subjects receiving radiation dose of 5000 cGy. The prevalence of dry desquamation for oily skin type was consistently greater in the control arm from day 21 after start radiotherapy (Figure 4).
Whereas, when subjects receiving radiation dose of 7000 cGy, subjects in the experimental arm experienced significantly lesser incidence of confluent desquamation (67.7%) than those in the control arm (100%) \( (P = 0.026) \).

For subjects who received radiation dose of 5000 cGy and had chemotherapy, those in the control arm had a significantly greater incidence of dry desquamation (82.4%) than those in the experimental arm (42.2%) \( (P = 0.008) \). Whereas, subjects who received radiation dose of 7000 cGy and had chemotherapy, there was no significant difference between both arms \( (P = 0.143) \).

Subjects who had booster radiation dose \( \geq 6500 \) cGy, there was also significant difference between the two arms \( (P = 0.004) \), the experimental arm experienced smaller incidence of dry desquamation (42.9%) than those in the control arm (86.7%). Whereas, subjects who received radiation dose of 7000 cGy and had
booster radiation dose of ≥6500 cGy, there was no significant difference between both arms \( (P = 0.86) \).

The Mann-Whitney U test for the worst skin reaction of confluent desquamation was significant difference between both arms \( (P = 0.021) \). The control arm suffered a longer period of time to change skin reaction from confluent desquamation to dry desquamation (more than 12 days) (Table 4).

**Table 4:**

<table>
<thead>
<tr>
<th>Duration from</th>
<th>Group</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>[Range]</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>onset of RT to erythema</td>
<td>control</td>
<td>25.79</td>
<td>5.74</td>
<td>28</td>
<td>14.42</td>
<td>0.002**</td>
</tr>
<tr>
<td></td>
<td>experimental</td>
<td>32.33</td>
<td>4.68</td>
<td>35</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>erythema to dry desquamation</td>
<td>control</td>
<td>7.37</td>
<td>4.35</td>
<td>7</td>
<td>21</td>
<td>0.743*</td>
</tr>
<tr>
<td></td>
<td>experimental</td>
<td>7.0</td>
<td>3.13</td>
<td>7</td>
<td>20.5</td>
<td></td>
</tr>
<tr>
<td>dry desquamation to confluent desquamation</td>
<td>control</td>
<td>18.79</td>
<td>9.35</td>
<td>14</td>
<td>24.68</td>
<td></td>
</tr>
<tr>
<td></td>
<td>experimental</td>
<td>13.48</td>
<td>9.66</td>
<td>14</td>
<td>16.71</td>
<td>0.024**</td>
</tr>
<tr>
<td>confluent desquamation back to dry desquamation after radiotherapy</td>
<td>control</td>
<td>19.16</td>
<td>11.63</td>
<td>21</td>
<td>24.87</td>
<td></td>
</tr>
<tr>
<td></td>
<td>experimental</td>
<td>12.1</td>
<td>4.94</td>
<td>14</td>
<td>16.55</td>
<td>0.021**</td>
</tr>
<tr>
<td>onset of skin reaction till RT finished and back to dry desquamation</td>
<td>control</td>
<td>50.11</td>
<td>9.41</td>
<td>56</td>
<td>27.16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>experimental</td>
<td>38</td>
<td>8.15</td>
<td>42</td>
<td>14.48</td>
<td>0.0**</td>
</tr>
</tbody>
</table>

* a, Mann-Whitney U test; *, significant at \( p<0.05 \)

**Skin Reaction Score 4 Weeks After Finishing Radiotherapy**

Subjects in experimental arm score grade 0 skin reaction was significant greater when compared with control arm \( (P = 0.001) \). The mean skin reaction score was 3.3 in the control arm whereas in the experimental arm was 0.95 (Figure 5).
Figure 5:

Skin reaction at each assessment

- Mean score of skin reaction
- Time from start radiotherapy (week)

- Control
- Experimental

P = 0.001 at week 11
Pain Level

In general, both arm developed more or less pain severity and frequency during each assessment. The median time for the subjects to have moderate radiation-induced skin soreness pain reaction (grade 3 or more) appeared in day 42 when subjects receiving radiation dosage of 60Gy. The cumulative probability of grade 3 or more pain was greater in the control arm (68.4%, n = 13) compared with those in the experimental arm (52.4%, n = 11) \( (P = 0.43) \) (Figure 6).

Figure 6:

![Chart showing cumulative probability of pain reaction across time from start radiotherapy (days)]

However, when subjects receiving 70Gy and finished radiotherapy after a week's time, i.e. at day 56, the cumulative probability of grade 5 or more pain was greater in the experimental arms (81%, n = 17) compared with control arm (73.7%, n = 14) \( (P = 0.93) \). The corresponding prevalence plots indicated that there was no significant difference between both arms (Figure 7).
After finishing the radiotherapy, the median time for control arm’s subjects to get less pain score (grade 2 or less) was in day 70 whereas in the experimental arm, the median time was in day 63. For experimental arm, there was significant difference in the cumulative probability of grade 2 or less pain compared with those in the control arm ($P = 0.045$).

For subjects who had concurrent chemotherapy, developed a greater incidence of pain (from grade 5 or more back to grade 2 or less) (88.2%, $n = 15$) compared with those who did not have chemotherapy (50%, $n = 1$) ($P = 0.257$). This difference did not reach the statistical significance. However, subjects who received chemotherapy in the control arm experienced a significantly greater cumulative probability of pain
(from grade 5 or more back to grade 2 or less) (88.2%, n = 15) compared with those in the experimental arm (35.7%, n = 5) ($P = 0.023$).

Subjects who had booster radiation dose $\geq 65$ Gy in the control arm experienced a significantly greater cumulative probability of pain (from grade 5 or more back to grade 2 or less) (93.3%, n = 14) compared with those in the experimental arm (35.7%, n = 5) ($P = 0.031$).

4 weeks after finishing radiotherapy, i.e. in day 77, the pain score 0 for experimental arm was greater (71.4%, n = 15) than the control arm (42.1%, n = 8). The mean pain score was 0.33 in the experimental arm whereas 0.89 in the control arm ($P = .024$).

The Mann-Whitney U test for duration of pain from the onset of pain till finishing radiotherapy and the subjects experienced less pain (grade 2 or less) between both arms was almost significant ($P = .002$). The control arm suffered a longer period of time to relieve the radiation pain (more than 38.5 days). However, for the duration of worst pain (grade 5 or more), there was no significant difference between the control arm and experimental arm ($P = 0.084$) (Table 5).
### Table 5:

**Comparison of the duration of Pain Score at each assessment by groups (control, n=19; experimental, n=21)**

<table>
<thead>
<tr>
<th>Duration of Pain score</th>
<th>Group</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>[Range]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain score grade 0</td>
<td>Control</td>
<td>29.47</td>
<td>7.22</td>
<td>28</td>
<td>17.79</td>
<td>0.141*</td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
<td>32.67</td>
<td>6.39</td>
<td>35</td>
<td>22.95</td>
<td></td>
</tr>
<tr>
<td>Pain score from</td>
<td>Control</td>
<td>13.26</td>
<td>7.34</td>
<td>14</td>
<td>21.42</td>
<td>0.607*</td>
</tr>
<tr>
<td>=&gt;grade 1 to =&gt;3</td>
<td>Experimental</td>
<td>11.67</td>
<td>5.57</td>
<td>14</td>
<td>19.67</td>
<td></td>
</tr>
<tr>
<td>Pain score from</td>
<td>Control</td>
<td>14</td>
<td>14.19</td>
<td>7</td>
<td>20.05</td>
<td>0.807*</td>
</tr>
<tr>
<td>=&gt;grade 3 to =&gt;5</td>
<td>Experimental</td>
<td>12.67</td>
<td>10.53</td>
<td>7</td>
<td>20.90</td>
<td></td>
</tr>
<tr>
<td>Pain score from</td>
<td>Control</td>
<td>16.58</td>
<td>10.49</td>
<td>21</td>
<td>23.76</td>
<td>0.084*</td>
</tr>
<tr>
<td>=&gt;grade 5 back to &lt;=2</td>
<td>Experimental</td>
<td>12</td>
<td>7.71</td>
<td>14</td>
<td>17.55</td>
<td></td>
</tr>
<tr>
<td>after finishing RT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain score from onset</td>
<td>Control</td>
<td>42.74</td>
<td>7.70</td>
<td>42</td>
<td>26.47</td>
<td>0.002**</td>
</tr>
</tbody>
</table>
| of RT till finished RT | Experimental| 33.33 | 8.25 | 35     | 15.10   |         | back to <= grade 2

*a*, Mann-Whitney U test; *, significant at p<0.05
Itching

The overall cumulative probability for developing itchy reaction was greater in the control arm than in the experimental arm at each itchy score assessment (Table 6).

Table 6:
Cumulative Probability of Itchy reaction at each assessment by group comparision:

<table>
<thead>
<tr>
<th>Grading of itchy reaction:</th>
<th>Control (n = 19) n (%)</th>
<th>Experimental (n = 21) n (%)</th>
<th>P value (Log rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itchy reaction grade 1 or more before day 35</td>
<td>15 (78.9%)</td>
<td>7 (33.3%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Itchy reaction grade 1 or more At or before day 35</td>
<td>19 (100%)</td>
<td>20 (95.8%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Itchy reaction grade 2 or more At or before day 35</td>
<td>15 (78.9%)</td>
<td>7 (33.3%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Itchy reaction grade 3 or more at or before day 42</td>
<td>14 (73.7%)</td>
<td>6 (28.6%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Itchy reaction back to grade 2 or less After finishing radiation at or before day 56</td>
<td>17 (89.5%)</td>
<td>11 (52.4%)</td>
<td>0.051</td>
</tr>
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4 weeks after completion radiotherapy, i.e. in day 77, the itchy score 0 for experimental arm was greater (85.7%, 18 of 21 subjects) than the control arm (42.1%, 8 of 19 subjects). The mean pain score was 0.14 in the experimental arm whereas 0.68 in the control arm ($P = 0.004$) (Figure 8).
For the duration of worst itchy reaction (grade 3 or more), the Mann-Whitney U test showed significant difference between the control arm and experimental arm ($P = 0.001$). The control arm suffered a longer period of time (more than 35 days) to relieve the radiation itchy reaction.

For subjects receiving 50 Gy, those who were oily skin experienced a significantly greater cumulative probability of grade 2 or more itching in control arm (60%, 3 of 5 subjects) when compared with experimental arm (0%, 0 of 6 subjects) ($P =0.034$). However, there was no significant difference between both arms for grade 3 or more itching when subjects receiving 60Gy or above in all kinds of skin type.

When subjects receiving the usual radiation dose 60Gy, those who had booster radiation dose $\geq$ 65 Gy in the control arm experienced a significantly greater
cumulative probability of itching (grade 3 or more) (80%, 12 of 15 subjects) compared with those in the experimental arm (28.6%, 4 of 14 subjects) ($P = 0.031$). After finishing radiotherapy, for the control arm, subjects who had booster radiation dose $\geq 65$ Gy experienced greater cumulative probability of itchy reaction (from grade 3 or more till radiation finish and back to grade 2) (86.7%, 13 of 15 subjects) compared with those in the experimental arm (50%, 7 of 14 subjects). There was no significant difference in itching between the two arms ($P = 0.065$).
Discussion

The findings of this study supported the hypothesis that aqueous cream with hydrogel was protective for radiation skin reaction in erythema and dry desquamation and reduced itchy. But it did not support the hypothesis that aqueous cream with hydrogel may be effective in reducing radiation pain and severe radiation-induced skin reaction, that was confluent desquamation when compared with the control arm which was used the standard regimen of applying nothing to the skin.

In Heggie et al. study (2002) found that aqueous cream was superior to aloe vera gel in reducing the acute radiation skin side effects of dry desquamation and pain, which found that topical cream or gel applied three times a day. Heggie et al. suggested that (2002, p.450) topical aloe vera gel might reduce erythema and might be beneficial in conjunction with aqueous cream for use on breast tissue undergoing irradiation. It was believed that the increased frequency of topical application and the use of aqueous cream in conjunction with hydrogel might be effective in reducing severe radiation-induced skin reaction of confluent desquamation and radiation-induced skin soreness pain

In this study, aqueous cream and amorphous hydrogel applied four times a day and the use of aqueous cream in conjunction with hydrogel were also applied. It was found to be significantly effective in reducing the incidence of erythema and dry desquamation and itching only. It was likely that the moisturizing effects of aqueous cream and amorphous hydrogel reduced skin from dryness and cracking which caused by repeated radiation. Boot-Vickers and Eaton (1999) asserted that the use of aqueous
cream could prevent the development of dry desquamation. This study also agreed with the study, which was done by Olsen et al. (2001): aloe vera gel was protective for radiation skin reaction. Crane (1993) reported that amorphous hydrogel had a soothing and cooling effect and could prevented skin break down. In Witt et al. study (1991) the use of water base gel had less purity and improved skin texture in the early stage of radiotherapy was also supported in this study.

The most important factor in the development of radiation-induced skin reaction, pain and itchy is radiation dose, and time period over which the dose is administered (McDonald, 1992). In this study, it was a standard treatment dose of 70 Gy with conventional fractionation (2 Gy over 35 minutes per treatment fraction, 5 fractions per week over 7 weeks). Other important factors of radiation skin reaction include the use of chemotherapy and boost radiation treatment. The higher the dose they received, the greater skin reaction, pain and itchy reaction. In this study, concurrent chemotherapy and the boost radiation treatment dose for the neck region were identical in both arms (median dose: 65Gy). Aqueous cream with hydrogel reduced the incidence dry desquamation at significance $P = 0.003$ compared with apply nothing to skin at radiation dose of 5000cGy. It was due to treatment. At cumulative dose of 7000cGy aqueous cream with hydrogel did not reduced the incidence of severe skin reaction in confluent desquamation compared with apply nothing to skin. It did not reach significance at the $P = 0.133$. There was association at time to skin change within cumulative dose of radiation. Within cumulative dose of radiation, new cell proliferation was inadequate or did not occur. In this moment, amorphous hydrogel did not have a good protection to the skin, thus confluent desquamation was evident.
Other important factors affected radiation skin reactions including the use of chemotherapy and boost radiation treatment. The variation in the severity of skin reaction experienced by individuals was often raised on several variables or factors. The factors were usually listed as: radiation dose, and chemotherapy administration (McDonald, 1992; Sitton, 1992).

For chemotherapy and boost radiation $\geq 6500$ cGy subjects, the aqueous cream with hydrogel experienced a significantly reduced incidence of erythema and dry desquamation when compared with subjects applied nothing.

Aqueous cream with hydrogel had a significant effect in delaying the time to first observed skin change, and itchy when compared with subjects apply nothing to skin. It proved that aqueous cream with hydrogel was protective for skin reactions. For the duration of worst skin reaction of confluent desquamation and itchy reaction of grade 3 or more, the experimental arm experienced a shorter period of time to relieve the radiation reaction (Table 4). The cumulative radiation dose increased over time, there was a protective effect of aqueous cream and amorphous hydrogel. Aqueous cream and amorphous hydrogel reduced skin dryness, crackling, and scaling (Sitton, 1992). The water-based gel had less purity.

An unexpected finding was the factor of oily skin type on the incidence of skin reaction had a significant protective effect for radiation-induced skin reaction. There was significant difference in the aqueous cream with hydorgel ($P = 0.026$)(Table 2) when compared with those applied nothing to skin at the cumulative radiation dose of 7000cGy for confluent desquamation. The reason behind this was unclear. It might be due to the fact that oily skin was caused by over-active glands, which produce a substance called Asebum, a naturally healthy skin lubricant. Oily skin could be slow
to develop discolourations, usually tans beautifully, rather than just burning and turning red. Oil-free moisturizer is benefit to oily skin from causing the upper layers of the skin to shrink and leading to blockages and breakouts (Loden, 2005). Aqueous cream and hydrogel are water based and oil-free base products. It might be a protective topical product for oily skin subjects undergoing radiotherapy.

The aqueous cream with hydrogel could not relieve radiation-induced pain when compared with subjects apply nothing to skin. The median time for the subjects to have moderate pain reaction (grade 3 or more) appeared in day 42 when subjects receiving radiation dosage of 60Gy. It was due to the fact that subjects experienced moist desquamation that was skin broken down. If skin broke down, the skin could be quite painful because of the exposure of nerve endings (Weiss, 2005). Amorphous hydrogel had a cooling effect and irritated the exposed nerve ending, thus those irritation caused subjects experiencing radiation skin soreness pain.

Subjects claimed that they applied their topical preparation 4 times a day. It was important that compliance was greater influence in prevention of radiation-induced skin reaction. The other difficulty was the determination of the amount of the topical preparation applied by each subject could be a factor influence the result.
Clinical Implication:

The result of skin care after innovative skin care procedures as per trial protocol might contribute to the formation of future radiotherapy skin care guidelines. It was hopefully beneficial in reducing radiation-induced skin reaction, including erythema, dry desquamation and itching toxicity.

Limitations of the Study and Future Research

It was a quasi-experimental study, there might be a bias resulted from the participants and observers by wishing the intervention to succeed.

The other limitation of this study was the failure to monitor the subjects at day 70 by the nurse. They were performed over the phone. It was because they did not need to return to the centre for treatment or follow up.

The result was only limited for the nasopharyngeal patients. It is not known whether it applies to other cancer patients. The products was effective within 5000 cGy; the evaluation of its optimum dose range be further study.

The sample size is too small. It only approached to 20% of meaningful power and need a large sample to prove the result. It was a quasi-experimental study. For further study, it needs a random controlled trial study to exclude the bias.
Oily skin had a significant protective effect for severe radiation-induced skin reaction of confluent desquamation, water base gel in conjunction with oil base topical product could be considered for future study.

**Conclusion**

Aqueous cream with amorphous hydrogel could reduce the radiation-induced skin reaction in erythema, dry desquamation and itchy within 5000cGy. There was a significant effect in delaying the time to first observed skin change, and itchy for the use of the products. The duration of worst skin reaction of confluent desquamation and itchy reaction, the experimental arm experienced a shorter period of time to relieve the radiation reaction.

Based on the study findings, oily skin has a better protection for the radiation-induced skin reaction, water base gel in conjunction with oil base topical product could be considered for future study.

There is a place for creams and gel in the prevention of radiation-induced skin reactions.
Reference:

Barkham AM. Radiotherapy skin reactions and treatments. Professional Nurse 1993;8:732–736.


Siddappa K. Dry skin conditions, eczema and emollients in their management. *Indian J Dermatol Venereol Leprol* 2003; 69:69-75


Appendix I:

Skin Care Guideline for Radiotherapy Skin Reaction

In the first week of the treatment, there is usually no obvious skin reaction. However, after two to three weeks of treatment, you will experience some observable skin reactions like reddening, itching, swelling, skin peel-off and hair loss (on treatment area).

In order to minimize the symptoms, the following skin care guideline should be observed:

- Clean your body as usual using lukewarm water to clean the treatment area. Don’t use cold or hot water. Avoid all kinds of soap. Pad dry with clean soft cloth. If the skin reaction becomes severe in the later stage of the treatment, you should not wash the treatment area.

- Avoid putting heating pads or ice packs on the treatment area.

- Don’t put any adhesive tape or apply ointment on the treatment area unless directed by the oncologist doctor or therapist.

- Avoid direct sunshine exposure of the treatment area. Protect your skin with caps, hats or umbrellas if necessary.

- Avoid irritating irradiated skin by keeping the area dry. In summer avoid excessive sweating by staying in a cool place or using an air-conditioner or electric fan.

- You should wear soft, loosely fitted clothing. Don’t wear clothes made of synthetic fibre to avoid skin allergy. This is especially important at and around your neck region. Avoid clothes with high or tight collars. Only use cotton or silk scarf if necessary.
• Avoid swimming during treatment period since salty or chlorinated water may worsen skin reaction.

• Use a towel to cover your neck when washing your hair.

• Don’t scratch the treatment area. Keep your fingernails short so as to avoid skin damage due to scratching subconsciously when sleeping.

• Use electric razor for shaving.

Finally, during all phases of radiotherapy, please feel free to consult your radiation oncologist, radiotherapist, or wound care nurse if you have any enquiry (Tel. 2835-).

SKIN CARE PROTOCOL FOR RADIATION THERAPY (Experimental Group)

Carry out the usual practice and include the following protocol.

ON THE FIRST TWO WEEKS AT THE TIME STARTING TREATMENT

(Date: ____________ to ____________ )

• Friction applied to the treated area should be minimized.

• Apply moisturizer cream (Aqueous cream) on the treatment area 4 times daily to protect skin from drying and have a cooling effect.

• Do not apply the moisturizer 2 hours before treatment.

ON THE THIRD AND FORTH WEEK OF THE THERAPY

(Date: ____________ to ____________ )

• Friction applied to the treated area should be minimized.
• Apply aqueous cream and hydrogel twice a day alternately on the treatment area. The gel is effective for protecting dry lesions and have a cooling effect also.

• Do not apply the gel 2 hours before treatment.

**ON THE FIFTH WEEK TO NINTH WEEK OF THE THERAPY**

(Date: ____________ to ____________)

• Friction applied to the treated area should be minimized.

• Apply hydrogel on the treatment area 4 times daily to protect skin from drying and have a cooling effect.

• Do not apply the moisturizer 2 hours before treatment.

**ON WEEK TEN AND ELEVEN AFTER THE COMPLETION OF THERAPY**

(Date: ____________ to ____________)

• Friction applied to the treated area should be minimized.

• Apply moisturizer cream (Aqueous cream) on the treatment area 4 times daily to protect skin from drying and have a cooling effect.
Appendix II

Radiotherapy Clinical Trial Topical Application Product

Aqueous Cream: (Figure 9)

It is made from a mixture of emulsifying ointment (which contains paraffin oils) and water, with phenoxyethanol as an antimicrobial preservative. It contains white soft paraffin BP 15%, liquid paraffin BP6%, emulsifying wax 9%, phenoxyethanol 0.5% and purified water BP to 100%

![Figure 9: Aqueous Cream](image)

Amorphous Hydrogel: (Figure 10)

![DuoDERM Hydroactive Gel](image)

A transparent watery gel with hydrocolloid formulation.
Appendix III

Demography Data

Patient's ID label

Height: 
Weight: 
BMI: 

Age: 

Sex: 

Skin texture: 

Diagnosis: 

RT dosage (primary tumour): 

RT dosage for neck node: 

Duration: _______________ Gy

5 fractions per week

Other treatment: 

with concurrent chemotherapy

without concurrent chemotherapy
Appendix IV

Skin Reaction Scoring System:

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<th>Score</th>
<th>Description</th>
<th>Date</th>
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<td>0</td>
<td>No changes noted</td>
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<td>1</td>
<td>Faint /dull erythema, follicular reaction</td>
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<td>2</td>
<td>Bright erythema</td>
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<td>3</td>
<td>Dry desquamation with or without erythema</td>
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<td>4</td>
<td>Small to moderate wet desquamation</td>
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<td>5</td>
<td>Confluent moist desquamation</td>
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<td>6</td>
<td>Ulceration, hemorrhage, or necrosis</td>
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Appendix V

Pain and Itchy Scoring System:

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<th>patient's ID label</th>
<th>pain score and itchy score</th>
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Zero represented no pain whereas 10 represented the worst.
**Itchy score**  
Zero represented no itchy whereas 5 represented the worst

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Appendix VI

INFORMATION SHEET

The effectiveness of local application of aqueous cream and amorphous hydrogel on radiated skin for patients with nasopharyngeal cancer who are undergoing radiotherapy.

You are invited to participate in a study conducted by Yu Sau Ling, who is MSc student of the School of Nursing in The Hong Kong Polytechnic University.

The goal of the study is aim at promoting skin integrity through early intervention.

Skin reaction – majority of patients will only experience mild degrees of reactions like skin reddening. Peeling of skin and itching. The irradiated skin may look as of it is sunburned, or tanned. But blisters, slough or ulcers may sometimes found in nasopharyngeal cancer.

The above side effects usually happen 2 or 3 weeks after starting treatment. The degrees of the side effects and the areas affected vary between individual patients and different radiation treatment schemes. The side effects will subside 3 to 4 weeks after the completion of radiation treatment in most cases.

Appropriate care minimizes the discomfort arising from radiation treatment and the patients will be more tolerant to their treatment. The course of treatment may be completed without any interruption.
During all phases of radiotherapy, the oncology nurse and the physician would carefully review your skin every week until two weeks after the completion of radiotherapy.

You have every right to withdraw from the study before or during the measurement without penalty of any kind. All information related to you will remain confidential, and will be identifiable by codes known only to the researcher.

If you have any complaints about the conduct of this research study, please do not hesitate to contact Mr. Eric Chan, Secretary of the Human Subjects Ethics Subcommittee of The Hong Kong Polytechnic University in person or in writing (c/o Human Resources Office in Room M1303 of the University).

If you would like more information about this study, please contact Yu Sau Ling at tel. no. 9688- or her supervisor Dr. Samantha Pang at tel. no. 2766-.

Thank you for your interest in participating in this study.

Name of investigator

Yu Sau Ling
Appendix VII

CONSENT TO PARTICIPATE IN RESEARCH

The effectiveness of local application of aqueous cream and amorphous hydrogel on radiated skin for patients with nasopharyngeal cancer who are undergoing radiotherapy

I __________________ hereby consent to participate in the captioned research conducted by Yu Sau Ling, Dr Samantha Pang is her supervisor.

I understand that information obtained from this research may be used in future research and published. However, my right to privacy will be retained, i.e., my personal details will not be revealed.

The procedure as set out in the attached information sheet has been fully explained. I understand the benefits and risks involved. My participation in the project is voluntary.

I acknowledge that I have the right to question any part of the procedure and can withdraw at any time without penalty of any kind.

Name of participant

________________________________________________________

Signature of participant

________________________________________________________

Name of researcher  Yu Sau Ling

Signature of researcher

________________________________________________________

Date

________________________________________________________
Appendix VIII

Ethical Approval from University

THE HONG KONG POLYTECHNIC UNIVERSITY

 guarda

Ref: EA/05/462

30 June 2005

To whom it may concern

This is to certify that approval has been given by the University in respect of the application for human subject ethics review of the following project:

Project Title: The Effectiveness of Local Application of Aqueous Cream and Amorphous Hydrogel on Radiated Skin for Patients with Nasopharyngeal Cancer who are undergoing Radiotherapy

Principal Investigator/Chief Supervisor:
Prof. Samantha Mei-che PANG

Co-investigator (including students):
YU Sau Ling

Should there be any subsequent changes in the proposal or procedures, which may affect the validity of the ethical approval, the Principal Investigator / Supervisor shall be responsible for obtaining fresh approval.

Shirley Ching (Dr.)
For & on behalf of
Departmental Research Committee
School of Nursing

Explanatory notes (PolyU Research Handbook, Section VI):
Principal Investigator/Chief Supervisor: The staff member who is responsible for the research/teaching project is the Principal Investigator. In the case of student research, the supervisor assumes this responsibility.
Co-investigator (including students): Other members of the project team.
Appendix IX

Ethical Approval from Hospital

Ms Yu Sau Ling, SS
Ward 15F

19th Aug, 2005

Dear Ms Yu,

RE: Research Study Application

Thank you for your research application.

I am pleased to inform you that the Hospital Research Committee has given your research team approval to carry out the following research project:

The effectiveness of local application of aqueous cream and amorphous hydrogel on radiated skin for patients with naso-pharyngeal cancer and breast cancer who are undergoing radiotherapy"

Please forward a copy of your report to the Research Committee for information and review upon completion of the project, or in 12 months time, whichever comes sooner. If this study will be published, please also provide information on its publication.

Yours Sincerely,

Dr Tsao Yen Chow
Chairman, Hospital Research Committee