

The Prevalence and Awareness of Regular Follow Up of Patients Treated with Phototherapy for Skin Cancer Surveillance

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Objective (Background): Regular full-body skin examination is commonly ignored in patients post-phototherapy, despite ultraviolet (UV) radiation being carcinogenic. Our objectives are to assess the prevalence of regular follow-up and full-body skin examination for patients treated with phototherapy, as well as the relationship between phototherapy exposure and the development of skin cancer in Saudi Arabia.

Methods (Settings, Design): This was a cross-sectional retrospective study conducted from January 2022 to July 2022. The study included 99 patients, selected via simple random sampling, from King Saud University Medical City, Riyadh, Saudi Arabia, who underwent phototherapy for at least 8 weeks and were followed for a minimum of 18 months post-treatment. Patients who met the inclusion criteria were called and given a questionnaire.

Results: Out of 99 patients, only 26 (26.26%) underwent full-body skin examinations by their physicians after phototherapy treatment. The average follow-up time after phototherapy was 3.2 years. Most study participants (85.85%) were unaware that cancer was a possible complication of phototherapy. Participants with knowledge about skin cancer complications were more likely to have undergone a full-body exam ($P = 0.001$). None of the participants developed any type of skin cancer after phototherapy.

Conclusion: Patients treated with phototherapy had no adequate information about the risk of skin cancer. The incidence of skin cancer was zero in our small cohort. Dermatologists in Saudi Arabia do not have an evidence-based notion regarding the risk of skin cancer among the Arab population after phototherapy. Since There is a lack of data examining the relationship between phototherapy and skin cancer in the Arab region, this study should trigger future studies with large populations and longer follow up periods.

Keywords: phototherapy, skin cancer, skin examination

Introduction

Phototherapy is an effective, widely-used method for treating some photosensitive skin diseases such as psoriasis, atopic dermatitis, mycosis fungoides, and vitiligo.^{1–5} However, ultraviolet (UV) radiation released from natural or ambient sources is carcinogenic,⁶ and is a major risk factor for nonmelanoma skin cancer in mice and humans.^{7–10} However, no studies have demonstrated an increased incidence of skin cancer in patients treated with broadband ultraviolet B (BB-UVB) (280–320 nm).¹⁰ The risk of developing cancer in narrowband ultraviolet B (NB-UVB), when compared to BB-UVB, is currently unknown. Mice studies have shown that NB-UVB induces skin tumors earlier than BB-UVB.^{1,7,9,11}

Different phototherapy strategies yield different results. Psoralen plus ultraviolet-A radiation (PUVA) is a known carcinogen in a dose-related pattern and may cause squamous cell carcinoma (SCC), but its relation to basal cell

carcinoma (BCC) has not been established. The carcinogenic risk of PUVA is not dose-related; other factors such as skin type, geographic location, and different treatment protocols must be considered. Three additional factors play a role in PUVA: history of arsenic exposure, skin cancer, and ionizing radiation therapy. Notably, using the USA protocol, men with skin types I and II treated with PUVA without protection of their reproductive organs have a higher risk of developing SCC of the penis and scrotum in a dose-related pattern.¹² PUVA-induced SCC appears to be less aggressive.^{13–19} Therapeutic UVB is associated with a small risk of skin cancer, except in cases of high UVB exposure (>300 treatments), which might increase the risk of genital tumors in men treated without protection.¹² Therefore, the risk of skin cancer associated with PUVA is well established, similar to that of BB-UVB phototherapy, but at a lower risk. Alternatively, the skin cancer risk associated with NB-UVB is still uncertain.²⁰ However, NB-UVB can theoretically induce more carcinogenic skin tumors than BB-UVB through the formation of Cyclobutane Pyrimidine Dimer.²¹

One study showed that patients treated with NB-UVB had no increased risk of SCC or malignant melanoma (MM), but had a significantly increased incidence of BCC versus controls.²² Retrospective studies conducted in Germany, Northern Ireland, and Scotland showed no evidence of the association of NB-UVB with the development of skin cancer. However, these studies in Caucasians may not be applicable to other races, because different races and skin colors react differently to UV radiation.^{1,6–24} Another retrospective study of 445 Korean patients treated with NB-UVB showed no significant increase in skin cancer in patients with skin phototypes III–V. One patient developed a 4-mm basal cell carcinoma on his leg by day 108 of treatment, but this seems unlikely to have been caused by NB-UVB phototherapy.²⁵

Methods

Study Design and Setting

This cross-sectional retrospective study was conducted between January 2022 and July 2022 and included 99 patients via simple random sampling from King Saud University Medical City, Riyadh, Saudi Arabia. Patients underwent phototherapy for a minimum of 8 weeks and were followed up for at least 18 months after their last treatment session.

Sample Size Determination

The sample size of 99 patients was determined using a single proportion formula: $(n = (z^2 P(1 - P))/d^2)$, where Z is the Z-score corresponding to a 95% confidence interval, P is the estimated prevalence (50%), and d is the desired precision (10%). This calculation resulted in a sample size of 97. To account for potential dropouts or withdrawals, we added 3 additional samples, resulting in a total sample size of 99 patients.

Data Collection

Data was collected from a review of medical charts and phone interviews conducted by three research assistants. A questionnaire was distributed to patients who met the inclusion criteria. To minimize bias, the interviewers underwent standardized training for interview questions. The questionnaire was validated through an in-depth review of the literature and professional opinion. Informed consent was given, and participants can withdraw from the research at any time without any obligation. Participants' anonymity was assured by assigning each participant a code number for analysis purposes only.

Questionnaire for Chart Review and Phone Interviews

The following factors were evaluated: sex, age, Fitzpatrick skin type, educational level, body mass index, income, household monthly expenses, employment status, type of housing, marital status, type of phototherapy received, age at the time of phototherapy, type of disease treated by phototherapy, duration of phototherapy, number of sessions per week, full-body exam done after phototherapy, knowledge about cancer as a possible complication, and development of skin cancer after phototherapy.

Participants in the Interview/Chart Review

The study included patients who received phototherapy in the dermatology clinic at King Saud University Medical City for a minimum period of 8 weeks and underwent phone interviews and medical chart reviews. Patients who missed their clinic appointments and did not complete 8 weeks of phototherapy were excluded from the study.

Ethical Consideration

The study adhered to ethical standards and was carried out after the approval of the Institutional Review Board (IRB) office at King Saud University with a Project approval No. (E-21-6258). Oral and written informed consent was obtained from all patients. The authors declare no conflicts of interest. All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. We confirm that informed consent was obtained from a parent or legal guardian for participants under 18 years of age.

Statistical Analysis

SPSS software version 26 was used for data entry and analysis. Descriptive statistics were calculated, including mean scores, standard deviations, and frequencies and percentages of all independent variables. Responses were scored as frequency and percentage, converted to percentage mean scores, and then transformed into qualitative data, as mentioned previously. Analytical statistics were applied using the chi-square test for qualitative data and Student's *t*-test and ANOVA for quantitative data, with $p < 0.05$ indicating statistical significance.

Results

The study included 99 patients, with their demographic data presented in Table 1. Regarding age, 60.6% were 16–45 years, 22.2% were >45 years, and 18.1% were <16 years. Among the study population, 54.5% were men, and 53.5%

Table 1 Patient Demographics

		Number of Patients (Frequency)
Age at the time of phototherapy (years)	0–15	18
	16–30	30
	31–45	30
	46–60	10
	>60	11
Gender	Male	54
	Female	45
Fitzpatrick Skin Type	Skin Type I	0
	Skin Type II	0
	Skin Type III	33
	Skin Type IV	61
	Skin Type V	5
	Skin Type VI	0
Marital Status	Married	53
	Single	46
Education	Secondary Education	41
	Bachelor	45
	Higher Education	13
Employment	Employed	42
	Housewife	14
	Retired	15
	Student	16
	Unemployed	12

were married. 61.6% were Fitzpatrick skin type IV, 33.3% were skin type III and 5% were skin type V. The most common level of education was a bachelor's degree (45.5%), and 42.4% were employed.

The clinical data and phototherapy details are presented in Table 2. Out of 99 participants, only 26 (26.26%) underwent a full-body skin examination after phototherapy treatment. All patients were immunocompetent. The average follow-up time after phototherapy was 3.2 years (range: 1.5–6 years). The most common disease treated with phototherapy was psoriasis (28.3%), followed by chronic pruritus (18.2%) and atopic dermatitis (15.2%). The most commonly used phototherapy type was narrowband (91.9%), and the most common duration was >4 months (52.5%). Most underwent three sessions per week (52.5%). The majority (85.85%) of the study participants were unaware that cancer was a possible complication of phototherapy. None of the participants developed skin cancer after phototherapy.

The relationship between the performance of the full-body exams and other parameters is shown in Table 3. Chi-square test revealed no statistical difference among males and females in the performance of full-body exams ($P = 0.404$), employment ($P = 0.11$), phototherapy duration ($P = 0.509$). Participants with knowledge about skin cancer complications were more likely to have undergone a full-body exam ($P = 0.001$).

The relationship between knowledge about cancer as a complication of phototherapy and other parameters is shown in Table 4. Chi-square test revealed no statistical difference in knowledge about skin cancer complications between males and females ($P = 0.712$) and among various educational levels ($P = 0.966$).

Thus, a substantial percentage of participants were completely unaware of skin cancer as a possible adverse effect of phototherapy.

Table 2 Clinical Data and Phototherapy Details

		Number of Patients (Frequency)
Disease treated	Psoriasis	28
	Chronic pruritus	18
	Atopic dermatitis	15
	Lichen Simplex Chronicus	7
	Mycosis Fungoides	3
	Pityriasis Lichenoides	3
	Chronica	
	Vitiligo	2
	Morphea	2
	Other	21
Phototherapy type	Narrowband	91
	PUVA	5
	Others	3
Duration of phototherapy	8 weeks	28
	12 weeks	19
	More than 12 weeks	52
Sessions per week	1 session	11
	2 sessions	35
	3 sessions	52
	More than 3 sessions	1
Full-body examination performed	Yes	26
	No	73
Knowledge about cancer as a possible complication	Yes	14
	No	85
Development of skin cancer after phototherapy	No	99

Table 3 Relationship Between Full-Body Examination Performance and Other Parameters

		Full-Body Examination Performance Number of Patients (Frequency)		
		Yes	No	P-value
Gender	Male	16	38	P= 0.404
	Female	10	35	
Employment	Employed	8	34	P=0.11
	Housewife	4	10	
	Retired	2	13	
	Student	10	6	
	Unemployed	3	9	
Phototherapy duration	8 weeks	6	22	P=0.509
	12 weeks	3	16	
	>12 weeks	17	35	
Knowledge about skin cancer complications	Yes	9	5	P=0.001
	No	17	68	

Table 4 Relationship Between Knowledge About Cancer Complications and Other Parameters

		Knowledge About Cancer as a Complication Number of Patients (Frequency)		
		Yes	No	P-value
Gender	Male	7	47	P= 0.712
	Female	7	38	
Education	Bachelor	6	39	P= 0.966
	Higher education	2	11	
	Secondary education	6	35	

Discussion

Phototherapy is one of the most effective treatments for several photosensitive skin diseases, such as vitiligo, psoriasis, and atopic dermatitis.^{1–5} However, it also emits UV radiation, which is a known carcinogen and a major risk factor for nonmelanoma and melanoma skin cancers in humans and mice.^{6–10} Although the relationship between phototherapy and skin cancers remains controversial, it is highly important for physicians to follow-up with patients receiving phototherapy, in order to assess the development of skin cancers. This study determined the prevalence of patients being followed up and examined by physicians for the development of skin cancer after receiving phototherapy in Saudi Arabia.

The association between phototherapy and skin cancer remains controversial. PUVA carries a well-established risk of skin cancer. In fact, a review article found that PUVA is a dose-dependent carcinogen which is also associated with other factors such as skin types I and II, geographical location, arsenic exposure, history of skin cancer, family history of skin cancer, exposure to ionizing radiation, and use of the USA protocol.¹² Specifically, PUVA was associated with an increased risk of SCC but not BCC.¹² Likewise, a prospective study of 1380 psoriasis patients treated with PUVA found that the number of PUVA treatments was strongly associated with an increased risk of SCC, in contrast to the risk of BCC.²⁶ In contrast, A study in 2012 showed that patients receiving PUVA had no increased risk of SCC or melanoma,²² but there was an increase in BCC versus controls.²² This increase might be due to diagnostic bias, wherein patients who were regularly followed up by their dermatologist had a greater chance of detecting skin cancer compared with those without regular follow-up.²² Type B UV is another type of phototherapy that is divided into broadband and narrowband,

which carry different risks for skin cancers. A retrospective study in Germany found that, out of 69 psoriasis patients treated with BB-UVB, none developed skin cancer (mean follow-up period: 93.6 months, range: 29–112 months; mean sessions 17.8).⁶ Moreover, Karaosmanoglu et al evaluated 100 patients who received whole-body NB-UVB, matched with 100 controls, and found no statistically significant difference in the development of skin cancer. Nevertheless, a high duration of NB-UVB treatment and a high cumulative dose of UV radiation can increase the risk of skin cancer.²⁷ Although NB-UVB phototherapy is effective for various skin conditions, it is essential to balance its benefits with the associated risk of skin cancer. Regular monitoring, dose management, and early detection through screening are crucial in managing this risk.

Our study showed that patients in our region treated with phototherapy were mostly not followed up with regular full-body examinations to screen for skin cancer. This lack of follow-up can be attributed to the notion that there is a minimal risk of skin cancer following phototherapy in our skin type. Thus, physicians may underestimate the importance of examining patients after phototherapy. To gain insight into this notion among physicians in Saudi Arabia, an expert panel discussion with more than 25 experienced dermatologists was conducted, and they all concurred that skin cancer was observed only in immune-compromised patients, aligning with the prevailing notion. However, this level of evidence is too weak to substantiate this claim. Nevertheless, some patients may develop unnoticed skin cancer that progresses to metastasis without appropriate follow-up and treatment.

Conclusion

Patients treated with phototherapy in our cohort had a significant lack of adequate information about the risk of skin cancer. In our small cohort, the incidence of skin cancer was zero. There is no evidence-based notion among dermatologists in Saudi Arabia regarding the risk of skin cancer among the Arab populations after phototherapy. Limitations in our study include its retrospective design, small sample size and short follow ups, but it should trigger future studies with large populations and longer follow up periods in our region as, to our knowledge, there is a lack of data on the prevalence and incidence of skin cancer in relation to phototherapy in the Arab region.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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