Int J Clin Exp Med 2020;13(6):3848-3856
www.ijcem.com /ISSN:1940-5901/IJCEM0107246

Review Article

Long-term efficacy of skin cancer surgery combined with 5-aminolevulinic acid-photodynamic therapy on facial skin cancer

Yifei Yang[1], Fang Wang[2,3], Ke Tian[4], Guoying Miao[1]

[1]*Dermatology of Affiliated Hospital of Hebei University of Engineering, Handan 056002, Hebei Province, China;* [2]*Nursing of Medical College of Hebei University of Engineering, Handan 056002, Hebei Province, China;* [3]*Respiration of Affiliated Hospital of Hebei University of Engineering, Handan 056002, Hebei Province, China;* [4]*CT of Affiliated Hospital of Hebei University of Engineering, Handan 056002, Hebei Province, China*

Received January 1, 2020; Accepted February 16, 2020; Epub June 15, 2020; Published June 30, 2020

Abstract: Objective: To evaluate the long-term efficacy of skin cancer surgery (SCS) combined with 5-aminolevulinic acid-photodynamic therapy (ALA-PDT) on facial skin cancer (FSC). Methods: A total of 110 FSC patients admitted to Affiliated Hospital of Hebei University of Engineering were enrolled, of which 60 patients were treated with SCS combined with ALA-PDT as a SAP group, and other 50 patients were treated with ALA-PDT alone as an AP group. The clinical efficacy, wound healing time, hospitalization time, wound infection rate, recurrence rate, living ability, social ability, psychological function, and body function of the two groups were compared, and the patients were followed up for 5 years, and compared in terms of the 5-year overall survival (OS). Moreover, the risk factors affecting treatment efficacy on FSC patients were analyzed. Results: The SAP group got better clinical efficacy, and experienced shorter wound healing time and hospitalization time than the AP group, and it also suffered a lower wound infection rate and recurrence rate than the AP group. In addition, the living ability, social ability, psychological function, and body function scores, and the 5-year OS of the SAP group were greatly higher than those of the AP group. Working under outdoor exposure, having organ transplantation experience, T stage, and treatment method were independent risk factors affecting the treatment efficacy on FSC patients. Conclusion: SCS combined with ALA-PDT has a definite long-term effect on FSC, so it is worthy of clinical promotion.

Keywords: Skin cancer surgery, ALA-photodynamic therapy, facial skin cancer, efficacy

Introduction

Skin cancer is the most common malignant tumor in the fair-skinned person, which has brought certain medical care burden to the society [1]. According to statistics, the incidence of skin cancer is on the rise, with 100,000 new cases each year in the United States alone [2]. The pathological types of skin cancer include the non-melanoma and melanoma of basal cell carcinoma and squamous cell carcinoma, of which non-melanoma skin cancer is the most common skin cancer in fair-skinned people, and is more common in men [3, 4]. Facial skin cancer (FSC) is a skin cancer on the face, and the cosmetic effect of treatment on it poses a great psychological impact on women [5]. Studies have shown that the most common cause of FSC is pathogenic mutation at the bispyrimidine site caused by excessive ultraviolet radiation, and sunscreen is of great importance in preventing FSC [6]. Skin cancer surgery (SCS) is the main treatment method for early FSC, and 5-aminolevulinic acid-photodynamic therapy (ALA-PDT) is a non-surgical treatment with relatively good cosmetic effect, but its side effects such as pain may lead to incomplete treatment [7, 8]. Therefore, this study compared the efficacy of SCS combined with ALA-PDT and that of ALA-PDT alone, with the goal ofproviding reference for treatment of FSC patients.

SCS, as a traditional treatment method for FSC, has certain clinical efficacy, but it may leave scars on the face of FSC patients and even

change their appearance, posing certain potential negative effect on the original appearance and mental health of them [9]. A study by Sanchez et al. [10] pointed out that the life quality of FSC patents within two weeks after SCS was not significantly improved, which implied that SCS alone may not be conducive to improving the short-term life quality of the patients after surgery. PDT is a centuries-old treatment with certain therapeutic effect on various benign diseases and even cancers, and it has advantages of non-invasion and ability of treating various diseases simultaneously [11, 12]. ALA is a prodrug required in PDT, and can be used for tumors including FSC [13]. Studies reported that in the mechanism of action of ALA-PDT for FSC patients, inhibition of the MAPK signaling pathway could intensify the toxicity of ALA-PDT on cancer cells and induce the death of the cells [14]. A study by Lu et al. [15] pointed out that ALA-PDT could be used as an auxiliary method of SCS, which was beneficial to narrow the resection range of FSC tumor lesions and had better safety and cosmetic effects. It implied that SCS combined with ALA-PDT may provide more satisfactory treatment efficacy on FSC patients.

At present, there are few studies on the long-term efficacy of SCS combined with ALA-PDT in the treatment of FSC patients, so we evaluated the efficacy of SCS combined with ALA-PDT by analyzing relevant indicators regarding clinical efficacy and long-term efficacy, hoping to provide clinical reference for the treatment of FSC patients.

Materials and methods

General materials

A total of 110 FSC patients admitted to Affiliated Hospital of Hebei University of Engineering from May 2013 to May 2014 were enrolled, of which 60 patients were treated with SCS combined with ALA-PDT as a SAP group, and other 50 patients were treated with ALA-PDT alone as an AP group. The SAP group consisted of 35 males and 25 females between 25 and 75 years old, with a mean age of 8.72±8.19 years, and the AP group consisted of 27 males and 23 females between 25 and 73 years old, with a mean age of 57.56±7.83 years. This study was approved by the Ethics Committee of Affiliated Hospital of Hebei University of Engineering, and study participants and their family members signed informed consent forms after understanding the study. The inclusion criteria were as follows: Patients diagnosed with FSC based on histology and pathology [16], patients willing to accept and cooperate with the therapeutic regimens of this study and willing to accept a 5-year follow-up, and those undergoing FSC treatment for the first time. The exclusion criteria were as follows: Patients comorbid with other malignant tumors or severe organ dysfunction, patients with mental disease and unable to communicate normally, patients with infectious disease, and those with recent history of surgery. The inclusion criteria were applicable to the SAP group and the AP group.

Treatment methods

SCS [17]: The skin in the entire skin lesion area was removed along the lateral side of the skin lesion edge according to the skin lesion. If the skin tension was not high, sutures were made directly, while if the skin tension was high, sutures were made after skin grafting or adjacent skin flap transfer.

ALA-PDT [18]: Patients were given ALA (Shanghai Yuduo Biotechnology Co., Ltd., China, YDM9280) as follows: 20% ALA was applied to the skin lesion according to the skin lesion area of the patients. A photodynamic laser therapeutic instrument (Tianjin Leiyi Laser Technology Co., Ltd., China, 3241235) was employed to radiate the skin lesion with red light for 20 minutes, with fiber pigtail 10 mm away from the skin lesion after the patient was in the dark for 3 hours, and the skin lesion was irradiated with 635 nm and 60-100 J/cm^2 for 30 min. The treatment was performed four times, once a week.

The SAP group was treated with SCS combined with ALA-PDT, with ALA-PDT performed after SCS, while the AP group was treated with ALA-PDT alone.

Efficacy assessment

The efficacy of the two groups was analyzed according to the *Response Evaluation Criteria in Solid Tumours (RECIST)* after a half year of treatment [19]. Complete remission (CR) referred to the outcomes as follows: Completely disappeared tumor skin lesions, relieved pig-

Table 1. Baseline data of the two groups [n (%), mean ± SD]

Factor	n	The SAP group (n = 60)	The AP group (n = 50)	χ^2/t	*P*-value
Sex				0.208	0.648
Male	62	35 (58.33)	27 (54.00)		
Female	48	25 (41.67)	23 (46.00)		
Age (Y)				0.206	0.650
<60	59	31 (51.67)	28 (56.00)		
≥60	51	29 (48.33)	22 (44.00)		
Average age (Y)	110	58.72±8.19	57.56±7.83	0.755	0.452
Hypertension history				0.001	0.970
No	76	41 (68.33)	34 (68.00)		
None	34	19 (31.67)	16 (32.00)		
Diabetes mellitus history				1.737	0.188
No	72	36 (60.00)	36 (72.00)		
None	38	24 (40.00)	14 (28.00)		
Drinking history				1.907	0.167
No	65	39 (65.00)	26 (52.00)		
None	45	21 (35.00)	24 (48.00)		
Smoking history				0.420	0.517
No	69	36 (60.00)	33 (66.00)		
None	41	24 (40.00)	17 (34.00)		
Family history of melanoma				1.473	0.225
No	83	48 (80.00)	35 (70.00)		
None	27	12 (20.00)	15 (30.00)		
Sunscreen measures				1.604	0.205
No	70	35 (58.33)	35 (70.00)		
None	40	25 (41.67)	15 (30.00)		
Be fond of sunbathing or not?				0.443	0.506
No	61	35 (58.33)	26 (52.00)		
Yes	49	25 (41.67)	24 (48.00)		
Work under outdoor exposure or not?				2.761	0.097
No	85	50 (83.33)	35 (70.00)		
Yes	25	10 (16.67)	15 (30.00)		
Have received an organ transplant or not?				0.104	0.747
No	91	49 (81.67)	42 (84.00)		
Yes	19	11 (18.33)	8 (16.00)		
T stage				0.044	0.835
T_1/T_2	96	52 (86.67)	44 (88.00)		
T_3/T_4	14	8 (13.33)	6 (12.00)		
Pathological type				1.315	0.252
Basal cell carcinoma	68	40 (66.67)	28 (56.00)		
Squamous cell carcinoma	42	20 (33.33)	22 (44.00)		
Tumor diameter (cm)				1.275	0.259
<5	92	48 (80.00)	44 (88.00)		
≥5	18	12 (20.00)	6 (12.00)		

mentation, and no original pathological changes. Partial remission (PR) referred the outcome that the skin lesion was reduced by at least half the area of it, and non-remission (NR) referred to the result that the skin lesion was reduced by less than half the area of it. The effective

Table 2. Clinical efficacy of the two groups [n (%)]

Group	n	CR	PR	NR	Total effective rate
The SAP group	60	25 (18.75)	27 (33.75)	8 (22.50)	86.67
The AP group	50	11 (18.00)	24 (58.00)	15 (6.00)	70.00
χ^2 value	-	4.791	0.099	4.581	4.581
P-value	-	0.029-	0.753	0.032	0.032

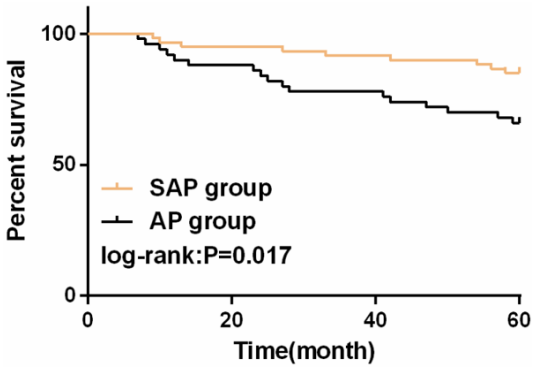

Figure 1. SCS combined with ALA-PDT was significantly associated with a higher 5-year OS.

rate = the number of patients with CR and that of patients with PR/the total number of patients × 100%.

Follow-up

The patients were followed up through telephone calls, visits and access to their pathological data for five years, four times a year. Overall survival (OS) refers to the time from confirmed diagnosis to death or the last follow-up day.

Other outcome measures

The wound healing time, hospitalization time, wound infection rate, recurrence rate, and adverse reactions of the patients were recorded.

The activity of daily living (ADL) scale and the General Quality of Life Inventory-74 (GQOU-74) were employed to evaluate life quality of the patients after surgery [20, 21]. The ADL scale was used for evaluation of the living ability, with a standard score between 0 and 100 points, and a higher score indicates better self-care ability. The GQOL-74 was used for evaluation of the social ability, psychological function, and body function, with 0 to 100 points, and a higher score indicates corresponding better evaluation.

Statistical analysis

In this study, the data were analyzed statistically using SPSS-22.0 (Beijing EASYBIO Technology Co., Ltd., China). Enumeration data were expressed as the number of cases/percentage (n/%). Inter-group comparison in terms of enumeration data was carried out using the chi-square test. Data with theoretical frequency in the chi-square test less than 5 were analyzed using the continuity correction chi square test. Measurement data were expressed as the mean ± standard deviation (mean ± SD), and inter-group comparison in terms of measurement data was carried out using the independent-samples T test, and comparison within groups was carried out using the paired t test. Logistics multivariate regression analysis was carried out to analyze risk factors for unfavorable prognosis of FSC patients. P<0.05 suggested a statistical significant difference.

Results

Baseline data of both groups are comparable

There was no significant difference between the two groups in terms of sex, age, average age, hypertension history, diabetes mellitus history, drinking history, smoking history, family history of melanoma, sunscreen measures, preference for sunbathing, working under outdoor exposure, organ transplantation experience, T stage, pathological type, and tumor size (all *P*<0.05). See **Table 1**.

The efficacy on the SAP group is significantly better

The evaluation revealed that the clinical efficacy in the SAP group was remarkably higher than that in the AP group (*P*<0.05). See **Table 2**.

The long-term efficacy on the SAP group is significantly better

We evaluated the long-term efficacy on the two groups undergoing different treatment methods according to the 5-year OS, and successfully followed them up for 5 years. It was turned out that the 5-year OS of the two groups was 76.36% (84/110), and the 5-year OS of the SAP group was significantly higher than that of the AP group (*P*<0.05). See **Figure 1**.

Table 3. Adverse reactions of the two groups [n (%)]

Item	The SAP group (n = 60)	AP group (n = 50)	χ^2 value	*P*-value
Scar hyperplasia	0 (0.00)	1 (2.00)	-	-
Scar contracture	0 (0.00)	2 (4.00)	-	-
Local edema	4 (6.67)	9 (18.00)	-	-
Severe itching	1 (1.67)	5 (10.00)	-	-
Serious pruritus	2 (3.33)	6 (12.00)	-	-
Total	7 (11.67)	23 (46.00)	16.208	<0.001

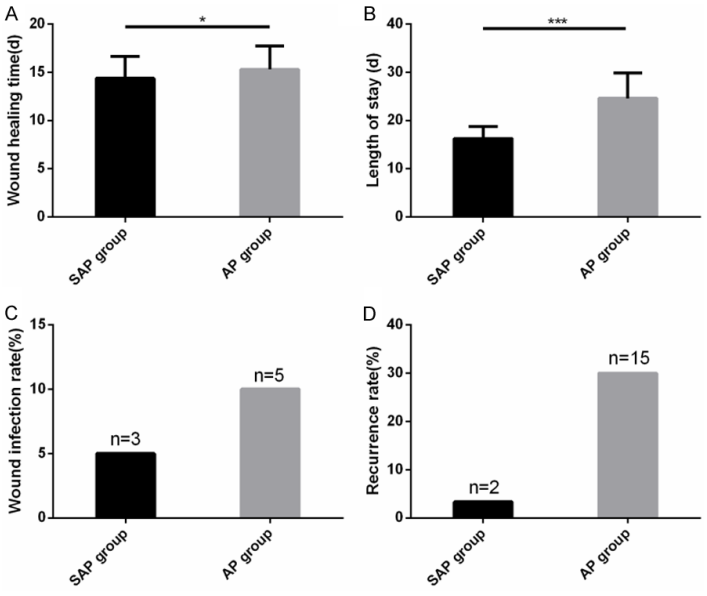

Figure 2. Relevant clinical indicators of the two groups. A. The wound healing time of the SAP group was remarkably lower than that of the AP group. B. The hospitalization time of the SAP group was remarkably lower than that of the AP group. C. The wound infection rate in the SAP group was remarkably lower than that in the AP group. D. The recurrence rate in the SAP group was remarkably lower than that in the AP group. Note: * indicates P<0.05, and *** indicates P<0.001.

The incidence of adverse reactions in the SAP group is significantly lower

The incidence of adverse reactions such as scar hyperplasia, scar contracture, local edema, severe itching, and serious pruritus in the SAP group was lower than that in the AP group, and the total incidence of adverse reactions in the SAP group was greatly lower than that in the AP group (*P*<0.05). See **Table 3**.

The recovery of the SAP group was significantly better

The SAP group experienced significantly shorter wound healing time and hospitalization time (P<0.05), and suffered a lower wound infection rate and recurrence rate than the AP group. See **Figure 2**.

The life quality of the SAP group was significantly better

The living ability, social ability, psychological function, and body function scores of the SAP group were dramatically higher than those of the AP group (all *P*<0.05). See **Figure 3**.

ALA-PDT treatment alone is one of the risk factors affecting the efficacy on FSC

The comparison between patients with complete remission or partial remission and patients with non-remission in terms of clinical parameters and relevant indicators revealed that in this study, there were 87 patients getting complete remission or partial remission, and 23 patients getting non-remission. There was no significant difference between the patients with complete remission or partial remission and patients getting non-remission in terms of sex, age, average age, hypertension history, diabetes mellitus history, drinking history, smoking history, family history of melanoma, preference for sunbathing, pathological type, and tumor size (all *P*>0.05), while there was a big difference between them in sunscreen measures, working under outdoor exposure, organ transplantation experience, T stage, and treatment method (all *P*<0.05). Multivariate logistic regression analysis was carried out to factors with differences, and it was turned out that working under outdoor exposure *(P* = 0.001), organ transplantation experience (*P* = 0.024), T stage (*P* = 0.018), and treatment method (P = 0.008) were independent risk factors affecting the treatment efficacy on FSC patients. Therefore, patients who worked under outdoor exposure, underwent organ transplantation, had high T stage, and received ALA-PDT treatment alone faced an increased risk of non-remission. See **Tables 4**-**6**.

Discussion

Basal cell carcinoma and squamous cell carcinoma are the main pathological types of FSC

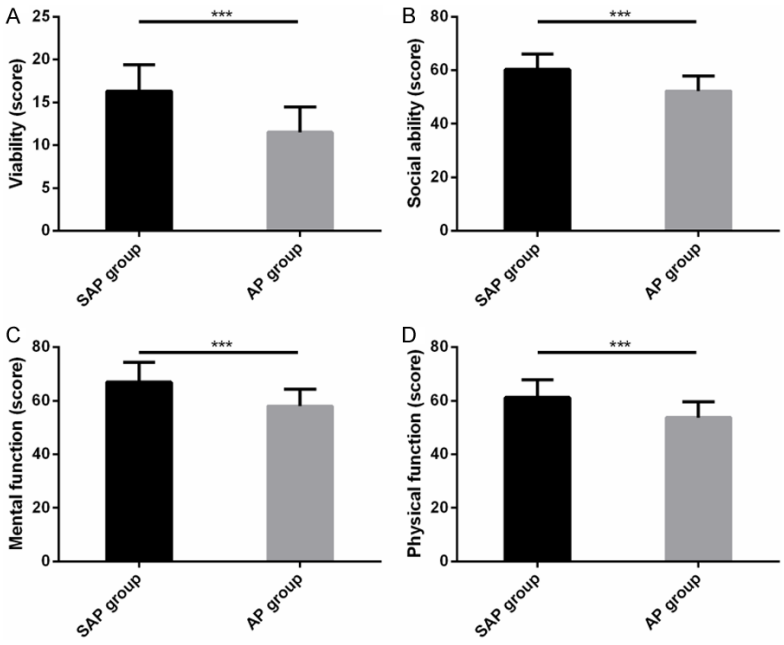

Figure 3. Comparison between the two groups in life quality. A. The living ability score of the SAP group was remarkably higher than that of the AP group. B. The social ability score of the SAP group was remarkably higher than that of the AP group. C. The psychological function score of the SAP group was remarkably higher than that of the AP group. D. The body function score of the SAP group was remarkably higher than that of the AP group. Note: *** indicates P<0.001.

patients in this study. Skin basal cell carcinoma is characterized by slow growth and small metastasis, which causes local tissue damage of patients and further leads to tissue dysfunction and appearance damage [22], and squamous cell carcinoma will increase the risk of recurrence and death of FSC patients when developing to affect lymph nodes [23]. Studies have reported that basal cell carcinoma and squamous cell carcinoma are the first and second common FSC, respectively [24]. Therefore, it is of great significance to study the treatment of FSC patients with these two pathological types for the maintenance of the patient's appearance and the reduction of the mortality risk.

There are a growing number of studies regarding the treatment of FSC patients. For example, a study by Dixon et al. [25] showed that the incidence of postoperative hemorrhage was 0.7%, and advanced age, Warfarin therapy, surgical site in or around the ear, skin flap closure, and graft were risk factors affecting the postoperative hemorrhage after SCS. A study by Morton et al. [26] pointed out that ALA-PDT had the same effect as cryotherapy in treating skin basal cell carcinoma, had more prominent healing and cosmetic effects, was superior to 5-fluorouracil in treating skin squamous cell carcinoma, and was more safe. In this study, the short-term clinical efficacy on the SAP group was significantly better than that on the AP group, and the 5-year OS in the SAP group was also significantly higher than that in the AP group, which indicated that SCS combined with ALA-PDT had better short-term and long-term efficacy for FSC patients, and was beneficial to improve the 5-year survival rate of patients. It is understood that FSC can also be treated by pulsed Nd laser irradiation, which is the most effective treatment for T (1-2), N (0) and M (0) stage FSC [27]. In this study, we analyzed relevant clinical indicators of the two groups, finding that the SAP group experienced shorter wound healing time and hospitalization time, and suffered a lower wound infection rate and a recurrence rate than the AP group, which indicated that the recovery of FSC patients treated with both SCS and ALA-PDT was faster than that of those treated with ALA-PDT alone, and SCS combined with ALA-PDT contributed to a lower postoperative infection rate and a lower recurrence rate. We also evaluated the postoperative life quality of the two groups, finding that the living ability, social ability, psychological function, and body function scores of the SAP group were greatly higher than those of the AP group, which implied that SCS combined with ALA-PDT was much more effective in improving patients' life quality.

Studying the risk factors affecting FSC patients is helpful for us to find the prevention strategy against FSC. Studies have shown that the potential risk factors for FSC include frequent absence of sunscreen measures, low sensitivity of skin to ultraviolet rays, smoking, alcohol abuse, and working under outdoor exposure, so paying attention to sunscreen, reducing exposure to ultraviolet radiation, and living a healthy

Table 4. Univariate analysis of the efficacy on FSC [n (%), mean ± SD]

Factor	n	The complete remission + partial remission group (n = 87)	The non-remission group (n = 23)	χ^2/t	*P*-value
Sex				0.240	0.624
Male	62	48 (55.17)	14 (60.87)		
Female	48	39 (44.83)	9 (39.13)		
Age (Y)				0.395	0.530
<60	59	48 (55.17)	11 (47.83)		
≥60	51	39 (44.83)	12 (52.17)		
Average age (Y)	110	58.85±8.30	57.42±7.62	0.747	0.457
Hypertension history				2.151	0.142
No	76	63 (72.41)	13 (56.52)		
None	34	24 (27.59)	10 (43.48)		
Diabetes mellitus history				1.026	0.311
No	72	59 (67.82)	13 (56.52)		
None	38	28 (32.18)	10 (43.48)		
Drinking history				0.079	0.778
No	65	52 (59.77)	13 (56.52)		
None	45	35 (40.23)	10 (43.48)		
Smoking history				1.385	0.239
No	69	57 (65.52)	12 (52.17)		
None	41	30 (34.48)	11 (47.83)		
Family history of melanoma				3.340	0.068
No	83	63 (72.41)	20 (50.00)		
None	27	24 (27.59)	20 (50.00)		
Sunscreen measures				4.523	0.033
No	70	51 (58.62)	19 (82.61)		
Yes	40	36 (41.38)	4 (17.39)		
Be fond of sunbathing or not?				1.689	0.194
No	61	51 (58.62)	10 (43.48)		
Yes	49	36 (41.38)	13 (56.52)		
Work under outdoor exposure or not?				14.358	<0.001
No	85	74 (85.06)	11 (47.83)		
Yes	25	13 (14.94)	12 (52.17)		
Have received an organ transplant or not?				4.455	0.035
No	91	83 (95.40)	8 (34.78)		
Yes	19	4 (4.60)	15 (65.22)		
T stage				8.209	0.004
T_1/T_2	96	80 (91.95)	16 (69.57)		
T_3/T_4	14	7 (8.05)	7 (30.43)		
Pathological type				2.412	0.120
Basal cell carcinoma	68	57 (65.52)	11 (47.83)		
Squamous cell carcinoma	42	30 (34.48)	12 (52.17)		
Tumor diameter (cm)				2.009	0.156
<5	92	82 (94.25)	10 (43.48)		
≥5	18	5 (5.75)	13 (56.52)		
Treatment method				9.643	0.002
SAP	60	55 (63.22)	5 (21.74)		
AP	50	32 (36.78)	18 (78.26)		

Table 5. Assignment in Logistic multivariate regression analysis

Factor	Variable	Assignment
Sunscreen measures	X1	Yes = 0, No = 1
Work under outdoor exposure or not?	X2	No = 0, yes = 1
Have received an organ transplant or not?	X3	No = 0, yes = 1
T stage	X4	T_1/T_2 = 0, T_3/T_4 = 1
Treatment method	X5	SAP = 0, AP = 1

Table 6. Multivariate Logistic regression analysis of factors affecting treatment efficacy on FSC patients

Variable	B	S.E	Wals	*P*-value	OR	95% CI
Sunscreen measures	0.635	0.592	1.158	0.284	1.899	0.592-6.174
Work under outdoor exposure or not?	0.547	0.860	2.279	0.001	1.782	1.018-2.831
Have received an organ transplant or not?	1.123	0.485	5.342	0.024	3.081	1.180-7.705
T stage	2.003	0.688	5.287	0.018	2.850	1.253-6.985
Treatment method	2.098	0.801	7.017	0.008	7.996	1.735-37.056

life help us prevent FSC [28]. A study by Fortina et al. [29] pointed out that organ transplant recipients faced an increased risk of FSC, and heart transplantation recipients faced a higher risk of FSC than kidney transplant recipient. It also concluded that age over 40 years, light skin, and over 10,000 hours of sunlight exposure were risk factors for FSC in organ transplant recipients. There are also reports indicating that in FSC induced by heart transplantation, the incidence rate of squamous cell carcinoma increases, and sunshine exposure over 30,000 hours in a whole life is the largest risk factor, followed by solar keratosis [30]. At the end of our study, we analyzed the risk factors affecting the efficacy on FSC, and found that working under outdoor exposure, having organ transplantation experience, T stage, and treatment method were independent risk factors affecting the treatment efficacy on FSC patients, which indicated that FSC patients who worked under outdoor exposure, underwent organ transplantation, had high T stage, and received ALA-PDT treatment alone faced an increased risk of non-remission.

There is still a room for improvement in this study. For example, we can supplement an analysis on the postoperative aesthetic appearance of FSC patients and the patients' satisfaction with treatment, and we can also supplement a study on the pathological regulation mechanism of SCS combined with ALA-PDT treatment. We will carry out supplementary research from the above improvement points in the future.

To sum up, SCS combined with ALA-PDT has definite long-term effect on FSC, so it is worthy of clinical promotion.

Disclosure of conflict of interest

None.

Address correspondence to: Fang Wang, Nursing of Medical College, Hebei University of Engineering, No. 83, Congtai Road, Handan 056002, Hebei Province, China. E-mail: wang8410700706@163.com

References

[1] Apalla Z, Lallas A, Sotiriou E, Lazaridou E and Ioannides D. Epidemiological trends in skin cancer. Dermatol Pract Concept 2017; 7: 1-6.

[2] Singh RP and Agarwal R. Mechanisms and preclinical efficacy of silibinin in preventing skin cancer. Eur J Cancer 2005; 41: 1969-1979.

[3] Diepgen TL and Mahler V. The epidemiology of skin cancer. Br J Dermatol 2002; 146 Suppl 61: 1-6.

[4] Perera E, Gnaneswaran N, Staines C, Win AK and Sinclair R. Incidence and prevalence of non-melanoma skin cancer in Australia: a systematic review. Australas J Dermatol 2015; 56: 258-267.

[5] Caddick J, Green L, Stephenson J and Spyrou G. The psycho-social impact of facial skin cancers. J Plast Reconstr Aesthet Surg 2012; 65: e257-259.

[6] Armstrong BK and Kricker A. The epidemiology of UV induced skin cancer. J Photochem Photobiol B 2001; 63: 8-18.

[7] Lee EH, Klassen AF, Lawson JL, Cano SJ, Scott AM and Pusic AL. Patient experiences and out-

comes following facial skin cancer surgery: a qualitative study. Australas J Dermatol 2016; 57: e100-104.
[8] Cohen DK and Lee PK. Photodynamic therapy for non-melanoma skin cancers. Cancers (Basel) 2016; 8: 90.
[9] Vaidya TS, Mori S, Dusza SW, Rossi AM, Nehal KS and Lee EH. Appearance-related psychosocial distress following facial skin cancer surgery using the FACE-Q skin cancer. Arch Dermatol Res 2019; 311: 691-696.
[10] Sanchez N, Griggs J, Nanda S, Fayne R, Castillo D, De Bedout V, Meirson D and Nichols A. The skin cancer index: quality-of-life outcomes of treatments for nonmelanoma skin cancer. J Dermatolog Treat 2019; 1-3.
[11] Abrahamse H and Hamblin MR. New photosensitizers for photodynamic therapy. Biochem J 2016; 473: 347-364.
[12] Zeitouni NC, Oseroff AR and Shieh S. Photodynamic therapy for nonmelanoma skin cancers. Current review and update. Mol Immunol 2003; 39: 1133-1136.
[13] Quintanilha NP, Dos Santos Miranda Costa I, Freiman de Souza Ramos M, Campos de Oliveira Miguel N and Riemma Pierre MB. alpha-Bisabolol improves 5-aminolevulinic acid retention in buccal tissues: potential application in the photodynamic therapy of oral cancer. J Photochem Photobiol B 2017; 174: 298-305.
[14] Ge X, Liu J, Shi Z, Jing L, Yu N, Zhang X, Jiao Y, Wang Y and Li PA. Inhibition of MAPK signaling pathways enhances cell death induced by 5-Aminolevulinic acid-photodynamic therapy in skin squamous carcinoma cells. Eur J Dermatol 2016; 26: 164-172.
[15] Lu YG, Wang YY, Yang YD, Zhang XC, Gao Y, Yang Y, Zhang JB and Li GL. Efficacy of topical ALA-PDT combined with excision in the treatment of skin malignant tumor. Photodiagnosis Photodyn Ther 2014; 11: 122-126.
[16] Calin MA, Parasca SV, Savastru R, Calin MR and Dontu S. Optical techniques for the noninvasive diagnosis of skin cancer. J Cancer Res Clin Oncol 2013; 139: 1083-1104.
[17] Dixon AJ, Dixon MP, Askew DA and Wilkinson D. Prospective study of wound infections in dermatologic surgery in the absence of prophylactic antibiotics. Dermatol Surg 2006; 32: 819-826.
[18] Ji J, Fan Z, Zhou F, Wang X, Shi L, Zhang H, Wang P, Yang D, Zhang L, Chen WR and Wang X. Improvement of DC vaccine with ALA-PDT induced immunogenic apoptotic cells for skin squamous cell carcinoma. Oncotarget 2015; 6: 17135-17146.
[19] Jerjes W, Hamdoon Z and Hopper C. Photodynamic therapy in the management of basal cell carcinoma: retrospective evaluation of outcome. Photodiagnosis Photodyn Ther 2017; 19: 22-27.
[20] Rozzini R, Frisoni GB, Bianchetti A, Zanetti O and Trabucchi M. Physical performance test and activities of daily living scales in the assessment of health status in elderly people. J Am Geriatr Soc 1993; 41: 1109-1113.
[21] Kuang WH, Li J, Ma YG and Liao J. Survey on psychologic status and quality of life for HIV infected people or AIDS patients. Sichuan Da Xue Xue Bao Yi Xue Ban 2005; 36: 97-100.
[22] Kauvar AN, Cronin T Jr, Roenigk R, Hruza G and Bennett R; American Society for Dermatologic Surgery. Consensus for nonmelanoma skin cancer treatment: basal cell carcinoma, including a cost analysis of treatment methods. Dermatol Surg 2015; 41: 550-571.
[23] Stratigos A, Garbe C, Lebbe C, Malvehy J, del Marmol V, Pehamberger H, Peris K, Becker JC, Zalaudek I, Saiag P, Middleton MR, Bastholt L, Testori A and Grob JJ; European Dermatology Forum (EDF); European Association of Dermato-Oncology (EADO); European Organization for Research and Treatment of Cancer (EORTC). Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. Eur J Cancer 2015; 51: 1989-2007.
[24] Kauvar AN, Arpey CJ, Hruza G, Olbricht SM, Bennett R and Mahmoud BH. Consensus for nonmelanoma skin cancer treatment, part II: squamous cell carcinoma, including a cost analysis of treatment methods. Dermatol Surg 2015; 41: 1214-1240.
[25] Dixon AJ, Dixon MP and Dixon JB. Bleeding complications in skin cancer surgery are associated with warfarin but not aspirin therapy. Br J Surg 2007; 94: 1356-1360.
[26] Morton CA. The emerging role of 5-ALA-PDT in dermatology: is PDT superior to standard treatments? J Dermatolog Treat 2002; 13 Suppl 1: S25-29.
[27] Moskalik K, Kozlov A, Demin E and Boiko E. The efficacy of facial skin cancer treatment with high-energy pulsed neodymium and Nd: YAG lasers. Photomed Laser Surg 2009; 27: 345-349.
[28] Coups EJ, Manne SL and Heckman CJ. Multiple skin cancer risk behaviors in the U.S. population. Am J Prev Med 2008; 34: 87-93.
[29] Fortina AB, Caforio AL, Piaserico S, Alaibac M, Tona F, Feltrin G, Livi U and Peserico A. Skin cancer in heart transplant recipients: frequency and risk factor analysis. J Heart Lung Transplant 2000; 19: 249-255.
[30] Caforio AL, Fortina AB, Piaserico S, Alaibac M, Tona F, Feltrin G, Pompei E, Testolin L, Gambino A, Volta SD, Thiene G, Casarotto D and Peserico A. Skin cancer in heart transplant recipients: risk factor analysis and relevance of immunosuppressive therapy. Circulation 2000; 102: III222-227.