THE ROLE OF RADIOTHERAPY IN THE TREATMENT OF NON-MELANOMATOUS CANCERS OF THE SKIN

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Purpose **:** To evaluate the treatment results and analyze the prognostic factors of radiotherapy for skin malignancies.

Materials and Methods **:** From January 1994 to April 2004, 48 patients with malignant skin cancer received a complete course of radiotherapy at Changhua Christian Hospital. There were 22 males and 26 females, between 38 and 94 years old (median: 78 years). The numbers of patients in stage I to IV were 16, 21, 11, and 0, respectively. The subtypes of histology were Squamous cell carcinoma (SCC) in 27 patients (56.3%), and Basal cell carcinoma (BCC) in 21 patients (43.8%). The median tumor size was 3 cm. Tumors location was predominantly at nose (29.2%), scalp (25%), facial (18.8%), extremities (8.3%), ear (6.3%), eyelids (4.2%) and others (8.3%). The median radiation dose and total treatment days were 60 Gy and 48 days.

Results **:** The patients were followed up until October 2004. The median duration of follow-up was 26 months (range: 5.8 to 118.8 months). The 5-year overall survival and disease-free survival rate were 56.2 % and 37.8 %, respectively. Treatment failure included loco-regional relapse (8 patients), and distant metastasis (3 patients). In univariate analysis of variables with log rank test, AJCC stage, histology type and nodal metastasis were the significant prognostic factors ($P < 0.05$) for overall survival.

Conclusion **:** Radiotherapy is effective in treatment of skin cancers. Our data indicated that the overall survival, disease-free survival, cosmetic appearance and patient tolerance were good and feasible.

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Key words: Radiotherapy, Nonmelanoma skin cancer, Prognostic factors

INTRODUCTION

Epithelial skin cancers are the most common malignant tumor among the white population [2,12,18,20,22]. Cutaneous squamous cell carcinoma (SCC) and Basal cell carcinoma (BCC), together commonly called non-melanomatous cancers of the skin, account for

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around 90% of cutaneous malignancies [2,20,22]. Several treatment modalities are used in the therapy of these cancers, including surgical excision, Mohs micrographic surgery, cryosurgery, curettage electrodessication, and radiotherapy [2,6,14,17]. However, direct comparisons among the available options are lacking. Based on the previous experiences and available evidence, surgical excision is the major treatment for most non-melanomatous cancers of the skin, with cure rates up to 98% with proper margins [2,7,11,17].

The application of radiation therapy has been used for skin cancer for nearly a century [7,9]. Recent developments in the technology of administering radiation therapy have improved the efficacy to treat skin cancer with less toxicity. Radiotherapy has an important primary role in the preservation of normal tissue with better cosmetic results [5]. Radiation may also be employed in combination with other modalities to treat aggressive or recurrent lesions, close excision margin or in elderly patients who are unable to tolerate surgery or who have inoperable tumors [2,9,11].

The incidence of skin cancer in Taiwan was increasing recently. Most of these cases are related to ultraviolet light exposure from the sun [3]. The objective of this study is to evaluate the treatment results and analyze the prognostic factors of radiotherapy for skin malignancies in our institute.

METHODS AND MATERIALS

Patients

From January 1994 to April 2004, 48 patients with histologically confirmed basal cell and squamous cell carcinomas of the skin were enrolled in this study. The patient population consisted of 22 males and 26 females between 38 and 94 years old (median: 78 years). There were 27 patients with squamous cell carcinoma and 21 patients with basal cell carcinoma.

These patients were separated into 2 arms: Arm A, a total of 30 patients with previous history of excision was enrolled. Twenty seven patients were proved to have positive surgical margin, with five of them associated with lymph nodes metastasis. The others 3 patients were histological proved to have lymph nodes metastasis with free surgical margin. Arm B, individuals who refused surgical intervention or were unfitted for surgery (18 patients). Among these patients, 3 patients were clinically confirmed to have lymph nodes metastasis by CT scan examination.

Tumors were clinically staged according to the criteria published by American Joint Committee on Cancer (AJCC) in 2002 [1]. Sixteen patients had T1 lesions, 19 had T2 lesions, and 13 had T3 lesions. The primary tumor sites are listed in Table 1.

Treatment

All patients received external beam radiotherapy. Radiation therapy was delivered with a linear accelerator with multiple energies. Electron beam therapy was used in 36 patients (75%), megavoltage photon beam in 9 patients (18.8%), and a combination of electron and photon beam in 3 patients (6.2%). The treatment area was defined as the volume of the tumor plus microscopic extension; with a margin of 2 cm. Fractions of 1.8 Gy were delivered 5 days a week over a period of 5 to 8 weeks for a total dose of 46 to 77.4 Gy, with a median dose of 60 Gy.

Table 1. Anatomical Distribution of Skin Cancers

Site	No. patients / %
Nose	14 / 29.2
Scalp	12 / 25.0
Facial	9 / 18.8
Extremities	4 / 8.3
Ear	3 / 6.3
Eyelids	2 / 4.2
Others	4 / 8.3
Total	48 / 100

Follow up

The patients were followed up until October 2004. All patients had been followed up for at least 5.8 months and 18 patients expired during the end of this study. Eight patients death were related to skin cancer (5 from the local recurrence group and 3 from the distant metastasis group) whereas the other 10 patients death resulting from other cause. The time of relapse-free survival was calculated from the completion of radiation therapy. Patients were considered relapse-free, if no evidence of loco-regional disease or distant metastasis had been found at the last follow-up visit or death.

Cosmetic results were evaluated according to pigmentation change, fibrosis or telangectasis existed. Excellent cosmesis was defined as no skin pigmentation or no fibrosis. A patient with slight pigment change or mild to moderate fibrosis is considered as good cosmesis, poor cosmesis was defined as severe fibrosis or skin contracture [5]. Skin reaction was also evaluated according to RTOG scale of toxicity [7,8].

Statistical analysis

Overall survival and disease-free survival were the primary endpoint of the analysis. Survival rate was estimated by using Kaplan-Meier methods, while the log-rank test was used to analyze differences between multiple survival curves.

Overall survival was defined as the time from completion of radiotherapy to death resulting from any cause. Patients who were alive were classified as censored observation at the time of last follow-up for overall survival. Disease-free survival was defined as the time from completion of radiotherapy to local failure, nodal failure, systemic failure or death resulting from any cause, whichever occurred first. Patients who got complete tumor response and were alive without local failure or systemic failure were classified as censored observations at the time of last follow-up for disease-free survival.

RESULTS

The median follow-up time was 26 months (range: 5.8 to 118.8 months). The 5-year and 8-year overall survival rates were 56.2% and 43.6%, respectively [Fig. 1]. The 5-year local tumor control rate was approximately 77.5% [Fig. 2] and the disease-free survival rate at 5-year was 37.8% [Fig. 3]. In addition, the 5-year disease-free survival rates for subgroup, Arm A and Arm B were 40.8% and 32.6% respectively [Fig. 4].

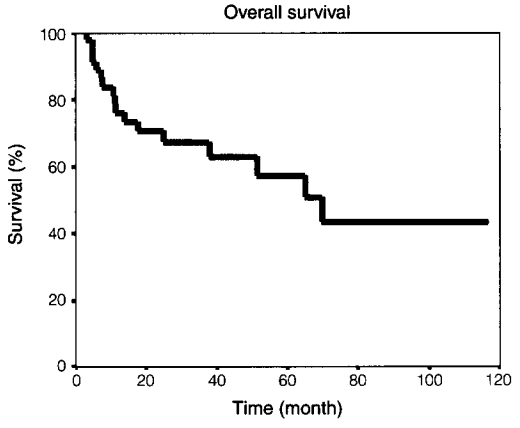

Fig 1. Overall survival curve of the patients with skin cancer (n = 48).

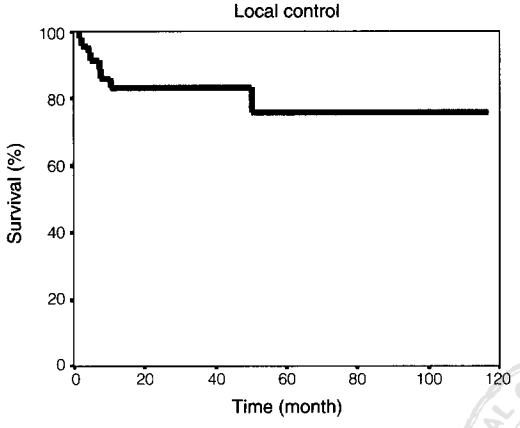

Fig 2. The local control of patients with skin cancer (n = 48).

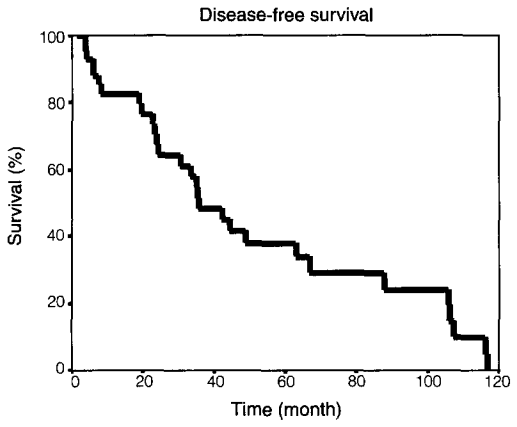

Fig 3. The 5-year disease-free survival rate.

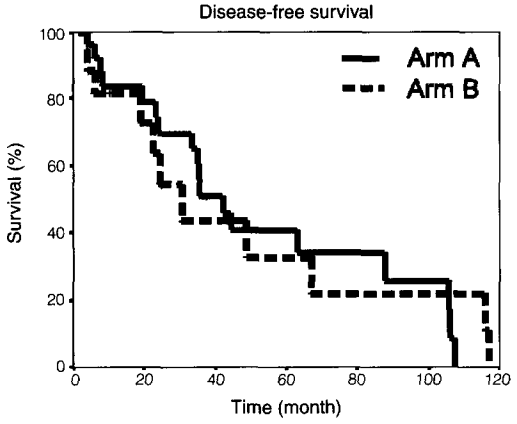

Fig 4. The 5-year disease-free survival rates of Arm A and Arm B were 40.8% and 32.6%, respectively.

A total of 11 out of 48 patients developed a loco-regional failure (8 patients) or distant metastases (3 patients). All of the eleven patients had a diagnosis of squamous cell carcinoma. The local control rate for Arm A and Arm B were approximately 80% and 88.8% respectively.

Larger lesions tended to have poorer local tumor control. In the group of patients who suffered from local recurrence, smaller tumors (size smaller than 3 cm) had a local recurrence rate of 9.0%, versus a local recurrence rate of 34.6% for larger tumors. Tumor size smaller than 3 cm exhibited a trend for better tumor control and overall survival, but there was no statistical significance.

For the patients who had positive surgical margin (Arm A), the local recurrence rate was 24.1%. Furthermore, patients that noted to have lymph nodes metastasis, the local recurrence rate had increased up to 70.0%. Meanwhile, among the patients who received definitive radiotherapy (Arm B), the local recurrence rate was 11.1%.

Most of the patients included in our study were proved to have positive surgical margin but there was no significant influence upon local tumor control. However, among the patients who suffered from lymph nodes metastasis, our results disclosed a statistically significant impact on overall survival. The radiation doses delivered also played a major role in overall survival. Total dose more than 60 Gy yielded a better tumor control rate and overall survival.

Univariate analysis of prognostic factors was performed by the log-rank test. The significant variables for overall survival included AJCC stage, histological type and lymph node metastasis [Table 2]. Cosmetic results [Table 3] and RTOG toxicity were recorded, too. The overall treatment-related toxicity of the electron beam therapy were better than the other treatment modalities [Table 4].

DISCUSSION

Skin cancer is readily diagnosed through routine physical examination and easily cured when it is detected early [11]. Adequate treatment at the initial presentation is critical. But, if an unsuccessful initial treatment is performed, it may carry a high morbidity and recurrence rate [14,17]. Multi-modalities are available for the treatment of non-melanomatous skin cancer. Among these, surgical excision and radiation therapy offer equivalent and high cure rates [17,19]. Various factors will influence the treat-

Table 2. Effects of prognostic factors on survival

Prognostic factor	No. of cases	5-year survival (%)	P-value
Gender			
Male	22	69.4	0.419
Female	26	47.5	
Histological type			
SCC	27	44.9	0.018
BCC	21	70.7	
LN metastases			
LN (+)	11	20.2	0.0049
LN (–)	37	66.24	
AJCC stage (2002)			
I	16	61.1	0.0043
II	21	60.5	
III	11	28.3	
Tumor size			
< 3 cm	29	59.3	0.189
> 3 cm	19	49.5	
Treatment Modality			
Photon	7	28.6	0.295
Electron	37	60.4	
Mixed beam	4	66.7	
Surgical Margin			
Margin (+)	27	61.8	0.454
Margin (-)	21	49.4	
Smoking			
Smoke(-)	31	48.3	0.410
Smoke(+)	17	70.3	
Radiation doses			
> 60 Gy	25	65.2	0.082
< 60 Gy	23	44.06	

ment decisions such as size and anatomic location of the lesion, involvement of adjacent tissue, depth of tumor invasion, tumor grade, and the general condition of the patients [14]. Based on the literatures, surgical intervention is the treatment of choice for the majority of these cancers [14,17]. The main goal of the treatment is complete removal of the primary tumor and any adjacent lesions that may be involved.

Liu et al. [10] showed a 5-year recurrence rate of 17% when the lateral margin was positive, and 33% when the deep margin was positive. Therefore, while ensuring adequate lateral excision margins, the surgeon must remain conscious of the depth of excision for preventing

Table 3. Cosmetic appearance correlated with the results of radiation for the nonmelanomatous skin cancer.

	Excellent Cosmesis	Good Cosmesis	Poor Cosmesis
No of the patient (n = 48)	15	24	9

Table 4. Treatment Related toxicities according to RTOG scale

	Electron	Photon	Mixed-beam
Grade 0	9	0	0
Grade 1	18	1	2
Grade 2	8	4	0
Grade 3	1	2	2
Grade 4	1	0	0
No of patients	37	7	4

treatment failure. Pascal et al. [15] had reported an excision strategy where the lateral excision margin versus the deep margin should be in the ration of 3 to 1. Moreover, the surgeon's skill and type of surgical technique may also be related to the treatment outcome [14,16,17].

Reynolds et al. [17] had demonstrated the margins necessary to ensure tumor clearance for both BCC and SCC. The researchers recommend that surgical excision of invasive SCC should include subcutaneous fat because 30% of the tumors extended into this layer [17]. Currently, margins for basal cell carcinoma range from 2 to 10 mm, and for squamous cell carcinoma, 4 to 15 mm was recommended [16,21]. Thomas et al. [21] also concluded that a 4 mm surgical margin should be excised for optimal treatment results. These figures show that the likelihood of recurrence is directly related to the adequacy of excision.

In addition to the adequate surgical margin, other relative risk factors associated with tumor recurrence and metastasis are the size and location of tumor. Alam et al. [2] reported that tumors larger than 2 cm may recur at a rate of 15.7% after excision, whereas for those with

size of 2 cm or smaller recur at a rate of 5.8%. Motley et al. [14] also found for larger tumors and high-risk locations (ear, lip, scalp, and nose) with wider margin (6 mm or more) should be removed. Under this condition, in order to improve treatment outcome, postoperative adjuvant therapy such as radiation therapy, systemic chemotherapy or immunotherapy should be applied [4,22].

Various retrospective studies concluded that when choosing a treatment modality, it is important to be aware of the factors that may influence outcome [14]. Postoperative radiotherapy, definitive radiotherapy or surgery alone provides a relatively high rate of tumor control. Postoperative radiation therapy is indicated for skin malignancies with close or tumor-involved surgical margins and lesions that recurred following other treatment modalities [2,7,17]. For those patients with incomplete resection of the tumor, involvement of regional lymph nodes, tumor with perineural invasion, tumor with potential aggressive or multicentric lesions, postoperative adjuvant irradiation is strongly suggested [9,13]. McCord and colleagues [13] had proved that surgery and radiotherapy provided a relatively high rate of local control for patients with perineural invasion. The issue about prophylactic nodal irradiation was discussed by Kwan et al. [9]and Alam et al. [2]. In British Columbia, the first echelon nodes in the radiation volume for T3 or T4 disease will be included. Our series showed that for patients suffering from lymph nodes metastases, up to 70% local recurrence rate was recorded. Therefore, prophylactic nodal radiation should be arranged, especially for those patients with high risk factors.

Definitive radiotherapy is another treatment modality for most of the skin cancer. It is a useful tool that can be used for elderly patients with extensive lesions when major surgery may not be appropriate [23]. Besides, among the lesions larger than 2 cm, lesions with deep infiltration and lesions with involvement of adjacent structures, in which surgery may result in poor outcome, radiotherapy is an alternative treatment modality. Furthermore, for small lesions located over lip, eyelid, ear, or nose, irradiation may offer an advantage over surgical technique with respect to cosmetic results and function [17]. Local tumor control, cosmetic results, and complication are mainly related to the size of the primary lesions, tumor location and depth of invasion. Radiation therapy is very effective in many situations. The control rate of majority of skin cancer treated with radiation alone is as high as 90% or more [7,17,23]

However, in our study the local control rate of patients who underwent radiotherapy alone (Arm B) was 88.8%, and that of patients who received postoperative radiotherapy (Arm A) was 80%. This result could be explained by several risk factors existed among the postoperative group of patient such as positive margin, lymph nodes metastasis and more advanced stage.

Another strategy for improving the locoregional control is administration of a higher dose of radiation. According to the guideline of Mallinckrort Institute of Radiology at Washington University, for the BCC lesions less than 1cm in size, 40 Gy is appropriate, and for lesions less than 3 cm or SCC less than 1cm in size, 45-50 Gy is recommended. For large BCC and SCC lesions, a total dose of 60 Gy is suggested [11]. Similar with this guideline, our data reflected that the dose exceeding 60 Gy could yield a better tumor control.

The adequate margin of irradiation may improve loco- regional control of patients with non-melanomatous skin cancer. In our institute, we used 2 cm or more as the margin of irradiation depending on tumor size and microscopic invasion. Locke et al. [11] reported that the minimum typical margin ranging from 2 to 3 cm was required.

The earliest applications of radiation therapy for skin malignancies were started soon after

the discovery of x-rays (x-ray machine) and gamma rays (radioactive isotopes)[5,7]. Superficial x-ray (250 kV) was introduced thereafter and has been gradually replaced by electron beams therapy since 1980s [5,7]. Nowadays, various forms of radiation therapy techniques are available, such as superficial x-ray, electron beams or megavoltage photon beams [11]. The electron beams have the advantage of more superficial isodose distribution. Besides, the electron beam also has less penetration than photon beams, and may be directed in a more adequate fashion for superficial treatments, while sparing deep tissues and reducing side effects [4]. Sometimes, bolus is required to enhance surface dose. The electron beam energy is selected based on delivering the treatment dose to the 80 to 90% isodose line. Griep et al. [5] had concluded that the use of electron beams is not inferior to superficial x-rays and even better for larger tumors. In our institute, most of the superficial lesions were treated by electron beam, whereas for bigger or deeper lesions, mixed beam may be beneficial.

The histological subtype was also found to be a statistically significant prognostic factor for local tumor control in our studies. Locke et al. [11] reported the squamous cell carcinoma of the skin had a higher incidence of recurrence (32%) and lymph nodes metastases (13%) compared with basal cell carcinoma. Demetrius et al. [4] also described the SCC tumors had potentially aggressive behavior that spreaded locally by infiltrating tissues. This tumor should be considered as high risk, and appropriate adjuvant therapy (e.g., lymph node dissection and postoperative radiation) should also be considered.

Tobacco smoking is a risk factor for several cancers such as the lung, bladder, and cervix, which has been studied extensively and is well established [20]. However, the effects of smoking on the development of the skin cancer are still less well known [9,20]. In our study, although half of our patients had the history of smoking, there was no significant statistic impact on the outcome.

CONCLUSION

Adjuvant radiotherapy was effective in eradicating microscopic residual tumors and could yield a good survival outcome for skin cancer in our study. Lymph node metastasis, stage, treatment response, local recurrence and histology type were the significant prognostic factors that may influence the loco regional control for skin cancer in our study.

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非黑色素皮膚癌接受放射治療之成果

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目的：本文旨在研究非黑色素皮膚癌在接受放射線治療後的結果，並分析影響治療結果的預後因子。

材料與方法：自 1994 年 1 月至 2004 年 4 月，共有 48 位病患在彰化基督教醫院診斷爲惡性皮膚癌並接受完整放射線治療療程。其中， 22 位爲男性， 26 位爲女性，歲數介於 38~94 歲（中位數爲 78 歲）。根據 2002 年 AJCC 分期系統，第 1 期至第 4 期病患人數分別爲 16 例、 21 例、 11 例及 0 例。在病理診斷方面， 27 例爲鱗狀細胞癌（56.3%），21 例爲基底細胞癌（43.8%）。腫瘤大小中位數爲 3 公分，腫瘤分佈分別爲鼻子（29.2%）、頭皮（25%）、四肢（8.3%）、耳（6.3%）、眼瞼（4.2%）及其他（8.3%）。放射治療爲一日一次，總劑量爲 55~70 Gy（中位數爲 60 Gy），平均治療時間 48 天。

結果：追蹤期從 6 個月至 120 個月不等（中位數爲 26 個月），此 48 位病患經放射線治療後的 5 年整體存活率爲 56.2% ， 5 年無病存活率 37.8% 。直至統計期限有 8 位病患局部復發，有 3 位遠端轉移。單變數分析結果指出腫瘤期別、組織病理型態及淋巴腺是否轉移此三變項，對整體存活率有顯著之影響（$P < 0.05$）。

結論：本研究結果顯示放射線治療在治療皮膚癌方面有顯著的效果。對於整體存活率、無病存活率、病患耐受度及美觀，也能達到令人滿意的結果。

[放射治療與腫瘤學 2006; 13(1): 1-9]

關鍵詞：放射治療、非黑色素皮膚癌、預後因子