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CLINICAL REPORT

Evaluation of Recurrence After Photodynamic Therapy with Topical Methylaminolaevulinate for 157 Basal Cell Carcinomas in 90 Patients

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The aim of this study was to evaluate the effect of photodynamic therapy with topical methylaminolevulinate for the treatment of basal cell carcinomas in a single dermatological department. Ninety patients (34.4% men and 65.6% women) with a total of 157 basal cell carcinomas (111 superficial, 40 nodular, 6 unknown) were treated. Primary endpoint was clinically observed recurrence verified by biopsy 3, 6 and 12 months after treatment, then once a year. Estimated patient recurrence rates were 7% at 3 months, 19% at 6 months, 27% at 12 months and 31% at 24 months. Patients aged over 60 years had significantly higher estimated recurrence rates compared with patients aged 60 years or under (at 12 months, 35% vs. 19%, $p=0.01$). Estimated recurrence rates for tumours was 4% at 3 months, 11% at 6 months, 16% at 12 months and 19% at 24 months. There were significantly higher estimated recurrence rates for nodular basal cell carcinomas compared with superficial basal cell carcinomas (at 12 months, 28% vs. 13%, $p=0.008$). In conclusion, photodynamic therapy is only appropriate for treatment of superficial basal cell carcinoma, and, age above 60 years and histology showing nodular basal cell carcinoma are independent risk factors for developing a recurrent basal cell carcinoma. ***Key words: basal cell carcinoma; photodynamic therapy; recurrence rate.***

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Basal cell carcinoma (BCC) is the most common malignant skin carcinoma, affecting more than 1 million people every year. The incidence of BCC is currently increasing by 10% per year worldwide (1). Metastasis of BCC is rare, with rates ranging from 0.0028% to 0.55% (2). A major challenge when treating BCC is the risk of local recurrence. Risk factors for recurrence include a tumour diameter greater than 2 cm, location on the central part of the face or ears, long-standing duration, incomplete excision, an aggressive histological pattern of growth, perineural or perivascular involvement, and immunosuppression (3). An estimated 40–50% of patients with a primary BCC will develop at least one or more BCC within 5 years (4). Clinically, BCC presents as superficial (sBCC), nodular (nBCC), infiltrating or morphoeic lesions. The morbidity is variable and, depends on factors such as localization and tissue invasion. In approximately 50% of cases, the lesion is seen in the head and neck area. When BCC infiltrate vital structures in the face, such as the eyes, ears, nose and mouth, mutilating surgery can cause devastating social and physiological disabilities, such as deafness, blindness and significant change in a person's appearance.

The most effective treatment for BCC is excisional surgery. Alternative treatment modalities are cryotherapy, imiquimod, curettage, radiotherapy and photodynamic therapy (PDT). When selecting the treatment for BCC, several aspects should be considered: histological subtype of the tumour; location and size of the tumour; age; and disability of the patient. PDT is often preferred for sBCC and thin nBCC when a good cosmetic outcome is desired and when the lesion is located outside the high-risk area (the H-zone of the face) (5). Selecting treatment for BCC often leaves the clinician with different treatment options: on the one hand patients with multiple low-risk tumours on visible sites of the body often request treatments with the best cosmetic outcome. On the other hand, the cure rate is important, especially regarding tumours located in areas of the body with a risk of high morbidity if the tumour recurs and infiltrates the surrounding tissue.

The aim of this retrospective study was to evaluate the efficacy of PDT with topical methylaminolaevulinate for BCCs. The fact that the results are based on clinical practise in a dermatological department at a university hospital, rather than on a clinical experimental study, makes them clinically relevant.

MATERIALS AND METHODS

Patients

All patients with histologically confirmed BCC (superficial, nodular, mixed superficial and nodular and infiltrative) treated with PDT in the period from January 2005 to April 2008 in the Department of Dermatology, Aarhus University Hospital, were enrolled. Treatment with PDT was chosen for patients with sBCC and thin nBCC when a good cosmetic outcome was considered important, and when other treatment modalities,

such as curettage, cryotherapy and imiquimod, were considered less favourable. Nodular lesions located in high-risk areas were treated with excision surgery or radiotherapy. For all patients, age, sex, number of tumours and number and dates of out-patient visits were recorded. For each tumour histology, localization, area (≤10 or >10 mm) and thickness (≤2 or >2 mm) were recorded. The study was approved by the Danish Data Protection Agency.

Design

The study is a retrospective, non-comparative study. Each tumour was treated twice, one week apart, with methylaminolaevulinate photodynamic therapy (MAL-PDT). After treatment, patients were followed up at 3, 6, 12 and 24 months.

Treatment

Before treatment, each tumour was prepared in order to facilitate access of methylaminolevulinate. The extent of preparation depended on the nature of the tumour. Superficial lesions were debrided with a curette to remove scales and crusts. The surface of the lesion was scraped gently in order to increase penetration of the active agent. Nodular lesions needed more radical preparation, including removal of intact skin covering the tumour by curettage. Methylaminolaevulinate (Metvix®; Photocure ASA, Oslo, Norway) 160 mg/g cream, approximately 1 mm thick, was applied on the lesion and 5 mm in the periphery of the tumour margins. The lesion area was then covered by adhesive, occlusive dressing for 3 h. After 3 h the occlusive materials were removed and the cream gently washed off with a 0.9% saline solution. The lesion area was illuminated with a red (570–670 nm) non-coherent light source (Curelight, Photocure ASA, Oslo, Norway), giving a total dose of 37 J/cm^2. Seven days after the first treatment, the procedure was repeated after removing the crusts. The treatment was performed by trained nurses after medical assessment by a dermatologist.

Endpoints

The primary endpoint was clinically observed recurrence verified by histology. A reappearance of a BCC in a previous PDT-treated area was defined as a recurrent tumour if it could be verified by histology. The patients were followed up 3, 6 and 12 months after treatment and then once every year. At each follow-up visit the treated areas were localized by comparing with photographs taken before treatment and were carefully investigated for clinical recurrence. Furthermore, all previously treated areas were easily localized using a standard illustration of the human body on which the tumours had been marked. Eighteen patients were discontinued before the first follow-up visit and 18 patients were discontinued after the first and before the second follow-up visit. In order to follow-up these 36 patients we searched the Danish Pathology Data Bank in February 2010.

Data analysis

Data were analysed initially by calculating time to recurrence for each patient separately, and then by calculating time to recurrence for each tumour separately. Multivariate Cox regression was used for statistical analysis. Initially, Cox regression with shared frailty, assigning the same (unknown) frailty to tumours from the same patient, was used to conclude that tumours from the same patient could be treated as independent with respect to recurrence in the Cox models. Recurrence rates over time were analysed using Kaplan–Meier failure estimates. p-values < 0.05 were considered statistically significant. Statistical calculations were performed using STATA version 11.0 (College Station, Texas 77845, USA).

RESULTS

Patients

Ninety patients (34.4% men and 65.6% women) with a total of 157 (111 sBCC, 40 nBCC, 6 histology missing) tumours were treated. The mean age was 62 years (age range 22−91 years). Fifty-one of the patients had one tumour, 11 had two tumours, and 28 had 3 tumours. Baseline characteristics for patients and lesions are shown in Table I. When analysing patients by a time to event approach the estimated recurrence rates were 7% at 3 months, 19% at 6 months, 27% at 12 months and 31% at 24 months. Patients aged over 60 years had significantly higher estimated recurrence rates compared with patients aged 60 years or under (at 12 months, 36% vs. 19%, $p = 0.01$) (Fig. 1). Multivariate Cox analysis showed that histology, area and localization did not have any impact on this difference. Sex did not influence the recurrence rate ($p = 0.98$).

Tumours

Estimated recurrence rate for tumours was 4% at 3 months, 11% at 6 months, 16% at 12 months, and 19% at 24 months. When comparing nBCC with sBCC there were significantly higher estimated recurrence rates for nBCC (at 12 months, 28% vs. 13%, $p = 0.008$) (Fig. 2). Although not statistically significant, we found that tumour area and thickness tended to increase recurrence. When comparing tumours localized in the face and scalp with tumours localized in other parts of the body there was no difference in recurrence rate ($p = 0.39$). Our data show that nBCC is more frequently located on patients with few tumours, whereas sBCC is more fre-

Table I. *Baseline characteristics of patients (*n = *90) and tumours (*n = *90)*

Characteristic	
Patients	
Gender, male:female, *n*	31:59
Age, years, mean (range)	62 (22−91)
Tumours (%)	
1 tumour	51 (57)
2 tumours	11 (12)
3 tumours	28 (31)
Histology (%)	
Superficial	111 (71)
Nodular	40 (25)
No histology	5 (3)
Missing	1 (1)
Localization (%)	
Face	112 (71)
Trunk	30 (19)
Extremities	7 (5)
Scalp	8 (5)

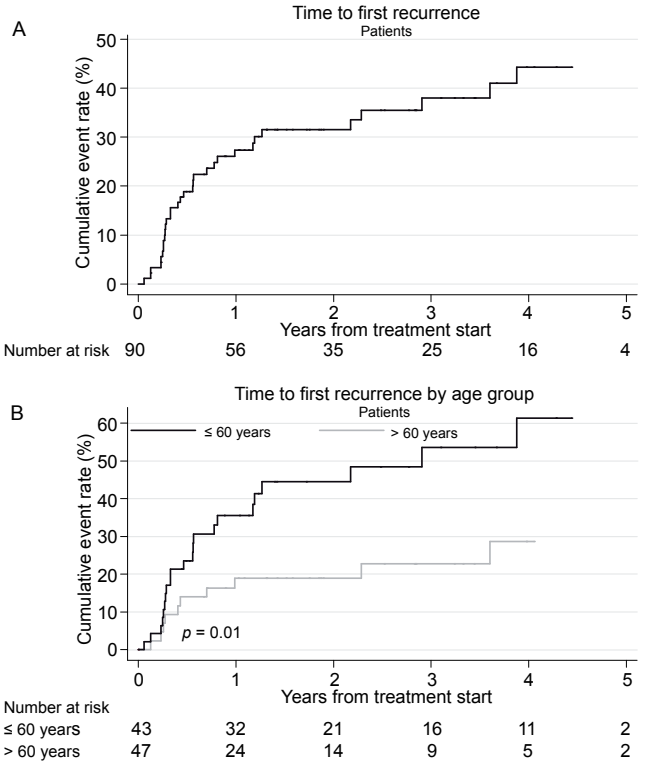

Fig. 1. Time to first recurrence after treatment of patients with basal cell carcinomas. (a) The estimated time to recurrence rates when analysing each patient separately. (b) The estimated time to recurrence rates when comparing patients >60 years of age (*black*) with patients ≤60 years of age (*grey*).

quently located on patients with more tumours ($p = 0.03$) (Table II). In addition, we found that patients with more tumours had a lower risk of tumour recurrence (33.3%, 27.3%, and 14.3% recurrent tumours for patients with one, 2 and 3 tumours, respectively) ($p = 0.03$).

DISCUSSION

This retrospective study confirms that recurrence is a problem when treating BCC with MAL-PDT. The estimated tumour recurrence rate was 19% 2 years after treatment. These findings are consistent with recurrence rates in randomized, prospective clinical trials (6–10). When comparing with these studies it is important to notice that three of these (6, 8, 10) allowed a second cycle of MAL-PDT after 3 months for those lesions with non-complete response. Interestingly, fewer recurrences were observed in the group of patients treated with repeated PDT cycles. In our study lesions without complete response after 3 months were categorized as recurrent. Compared with our results, one randomized controlled trial showed superior results for MAL-PDT sBCC after 12 months, where only 9.3% of the lesions had recurred (11). Another interesting study showed that long-term remission rate of fractionated ALA-mediated PDT of superficial BCC was significantly better than after PDT with single illumination (12).

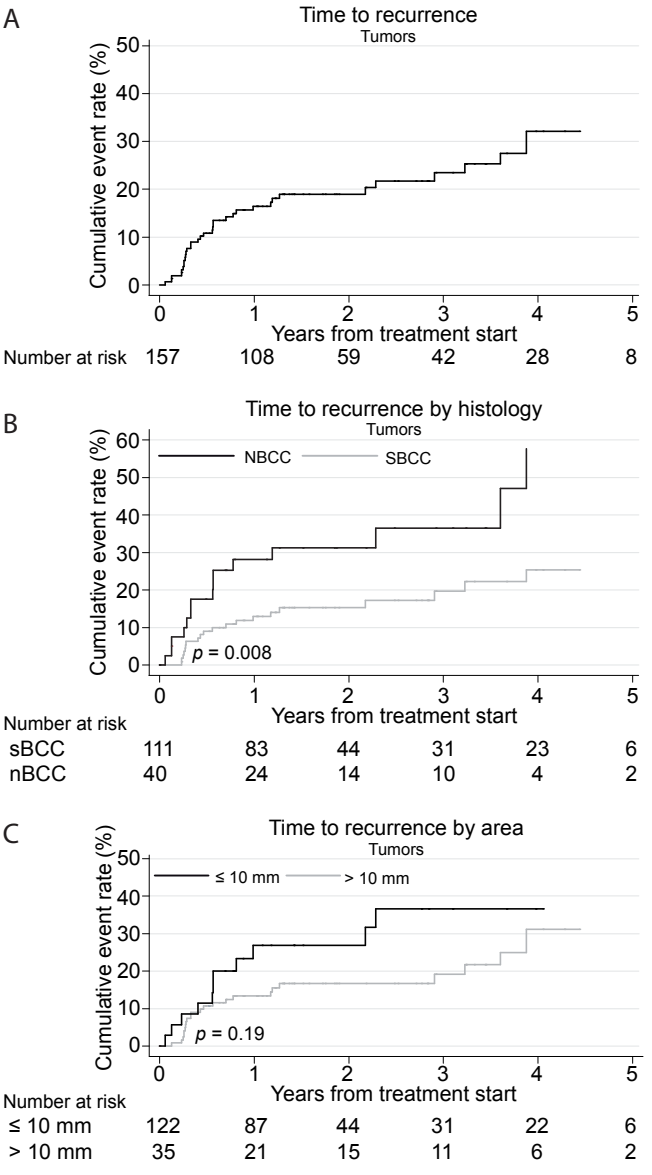

Fig. 2. Estimated time to recurrence rates for tumours. (a) Tumour recurrence rates for all 157 tumours. (b) Recurrence rates comparing superficial basal cell carcinoma (sBCC) (*grey*) with nodular basal cell carcinoma (nBCC) (*black*). (c) Influence of tumour area ≤10 mm (*grey*), >10 mm (*black*) on recurrence rate.

An important finding in the present study is that age above 60 years and histology showing nBCC are factors that increase recurrence. When comparing the patients above 60 years with those aged 60 years or under we found no difference in histology, area and localization of the lesions. This indicates that age is an independent risk factor for recurrence. Although malignancy can

Table II. *Tumour histology by total number of tumours for the patients (*p = *0.03)*

Histology	1 tumour	2 tumours	3 tumours	Total
Superficial basal cell carcinoma	31	20	60	111
Nodular basal cell carcinoma	19	2	19	40
Total	50	22	79	151

develop in all ages, the overall risk of developing cancer increases with age. Furthermore older age is known to be related to a worse response to treatments of many illnesses, including malignancy. Together, these facts can explain our findings. Moreover, histology showing nBCC was shown to be an independent risk factor for recurrence. The presence or absence of such risk factors should be taken into account when selecting therapy. We also showed that superficial lesions are more frequently located on patients with several tumours, and these lesions show a better response to PDT treatment compared with the nodular lesions.

A population-based cohort study showed that 53% of patients with BCC are females (13). Nevertheless, there was a majority of women (34.4% men and 65.6% women) in our cohort. A reason for this imbalance in sex ratio could be that women are more likely to choose PDT rather than other treatment options because of the better cosmetic results.

When comparing PDT and cryotherapy for treatment of sBCC, the effectiveness is similar, but PDT demonstrates superior cosmetic results (8). A 5-year follow-up study showed that excisional surgery of nBCC had a significantly higher complete response rate 5 years after treatment compared with PDT (7). Studies comparing PDT with imiquimod and curettage are still lacking.

In conclusion, these findings support the idea that PDT is preferable for thin BCC lesions. The fact that age over 60 years, in our cohort, independently increased the risk of recurrence, leads to the advice that age should be taken into consideration when treating BCC. Furthermore, we know that PDT has the advantage of good cosmetic outcome compared with other treatment options, such as cryotherapy, excisional surgery, curettage and radiotherapy. However, treatment with PDT should be reserved for tumours outside high-risk areas due to the high risk of recurrence.

The authors declare no conflicts of interest.

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