

CLINICAL REPORT

Factors Affecting the Recurrence Rate of Basal Cell Carcinoma

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The aim of this retrospective survey was to determine recurrence rates after treatment of basal cell carcinomas in a single academic dermatology department. A total of 1016 patients with 1593 histologically verified basal cell carcinomas ($n=1212$ primary and $n=381$ relapsing) were included. Tumour localization, T-stage and the method of treatment were significant predictors of the risk of recurrence (forward Cox regression, $p < 0.001$). The relapse rate for primary basal cell carcinomas on the scalp was highest (odds ratio (OR)=2.8, 95% confidence interval (CI) 1.5–5.3). T2 and T3 tumours showed a 2- and 3-fold increased relapse rate, respectively, compared with T1 basal cell carcinomas. Radiotherapy and surgical excision had the lowest relapse rates, whereas curettage and photodynamic therapy resulted in 5-year relapse rates of up to 70%. Patients with chronic skin diseases had a 50% lower risk of relapse than healthy patients (OR=0.5, CI=0.3–0.8). Recurrent basal cell carcinomas had a higher relapse rate than primary lesions (OR=1.8, CI=1.4–2.2). Patients treated in a specialized skin cancer unit had a 6.4-fold (CI=2.4–17.4) higher cure rate compared with those treated by less experienced physicians. Thus, in an uncontrolled, real-life situation curettage or photodynamic therapy are associated with significantly higher relapse risk than excision and radiotherapy and therefore should not be used for high risk primary tumours or recurrent tumours. Treatment in the setting of a specialized skin cancer unit yields a much lower relapse rate. *Key words: basal cell carcinoma; recurrence rate; risk factors; immunosuppression; surgical excision; curettage; radiotherapy; photodynamic therapy.*

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Basal cell carcinoma (BCC) is the most common skin neoplasm, with a 70% increase in incidence over the last three decades (1). Mortality rates due to BCC are low, but its high incidence and morbidity translates into a high economic burden (1). BCC can cause extensive destruction of tissue, particularly on the face (2) where early, radical treatment reduces scarring and disfigurement (3).

Earlier studies identified several prognostic factors that should be taken into account when choosing the appropriate treatment for BCC (4). Most (86%) of BCC are found in the head region, where the tumours are also most difficult to treat (3). The particularly high-risk areas are the central region of the face involving the inner canthus, nostrils, and peri-auricular area (3). Tumours on the scalp and forehead are considered to pose a middle risk of recurrence, whereas the low-risk areas comprise the neck, trunk and extremities (5). In addition to the localization, the tumour size (T stage) has prognostic significance (3). Tumour recurrence increases by approximately 7% for each millimetre of tumour diameter (6). Other factors are: male sex (7), sun-sensitive skin (8), age over 60 years at first presentation (8), histological type (4) and immunological status (9).

The presence or absence of risk factors is taken into consideration when choosing the therapeutic option. In Europe, especially in the UK, Scandinavia and France, curettage with or without cautery or simple excision are often the first choice of treatment, particularly for low risk tumours less than 1.5 cm in diameter. It has been argued that these simple and cheap techniques are adequate and probably preferable to the more costly Mohs micrographic surgery (MMS) (10–12). Several studies have demonstrated the very low recurrence rate of curettage, comparable to that of MMS and not exceeding 5% (13, 14). In other studies, however, the cure rate of curettage does not exceed 75% for the difficult to treat tumours (15–17).

Other treatment options comprise radiotherapy, photodynamic therapy (PDT), cryotherapy with liquid nitrogen or imiquimod. The selection among these of the therapeutic modalities depends on the predicted tumour aggressiveness and local preferences in different centres.

This study reappraised the importance of risk factors and treatment modality on the recurrence of BCC treated in an academic setting where MMS is not performed. The results suggest that the therapeutic outcome is often worse in real life than it could be deduced from the available clinical studies. In particular, treatment of higher risk facial tumours by curettage or PDT resulted in a surprisingly high 5-year recurrence rate when the treatment was performed by inexperienced physicians. The results also suggest how the treatment results by traditional modalities such as curettage or PDT may be improved.

MATERIALS AND METHODS

Patients and data capture

All patients treated for BCC in our institution in the period January 1998 to January 2005 were included in the study. In all cases the diagnosis was histologically proven. Patients were categorized as having multiple tumours if they presented with >2 tumours at the first consultation. For all patients their sex, age, number of primary and recurrent lesions, lesion localization and size, concurrent diseases, and the treatment modality were recorded. Whether the treatment took place in a specialized cancer treatment unit under the supervision of an experienced dermatologist was also recorded. After data collection we excluded 86 tumours treated with topical 5-fluorouracil (once daily, for 3 months or until development of skin ulceration), CO₂-laser, imiquimod or untreated tumours, due to the low number of individuals. Tumours were categorized into 3 groups: T1 tumours: <2 cm in diameter, T2 tumours: ≥2 cm to <5cm in diameter, and T3 tumours ≥5cm in diameter. The patients were also categorized into two groups: one group treated by a specialist in dermatology and the other by a physician in training.

Data analysis

For statistical analysis a forward Cox regression was used including the following variables: age, sex, tumour size, concurrent disease, presence of multiple tumours, treatment modality, localization and treatment in cancer treatment unit. Odds ratio (OR), 95% confidence intervals (CI) and *p*-values were calculated with SPSS software (version 13.0, SPSS Inc., Chicago, Illinois, USA). A *p*-value <0.05 was considered significant.

RESULTS

Factors determining the recurrence rate of primary BCC

A total of 1016 patients were identified (55.4% women and 44.6% men) presenting with 1593 tumours. A total of 1212 tumours were primary BCC and 381 tumours were the recurrent ones referred to our institution from private practice for further treatment. The mean age at the time of diagnosis was 73.3 years (range 23–102 years). Sixty-eight of the patients had multiple tumours (a total of 310 tumours) defined as >2 tumours at the first treatment. The probability of recurrence of primary BCC was analysed in 804 patients (1139 tumours) including these parameters, which showed significance in a single variable Cox regression model: tumour size and localization, choice of treatment, and concurrent disease.

As expected, tumour localization was strongly and independently correlated with the recurrence rate. Truncal carcinomas had the best prognosis, whereas carcinomas of the scalp had the highest risk of recurrence (OR 2.8, CI 1.5–5.3) (Fig. 1A). Stage T1 had the lowest recurrence rate, whereas stage T2 and T3 had OR for relapse of 2.0 (CI 1.4–2.8) and 3.1 (CI 1.4–6.8), respectively (Fig. 1B). Surgical excision and radiotherapy had excellent cure rates, whereas curettage and

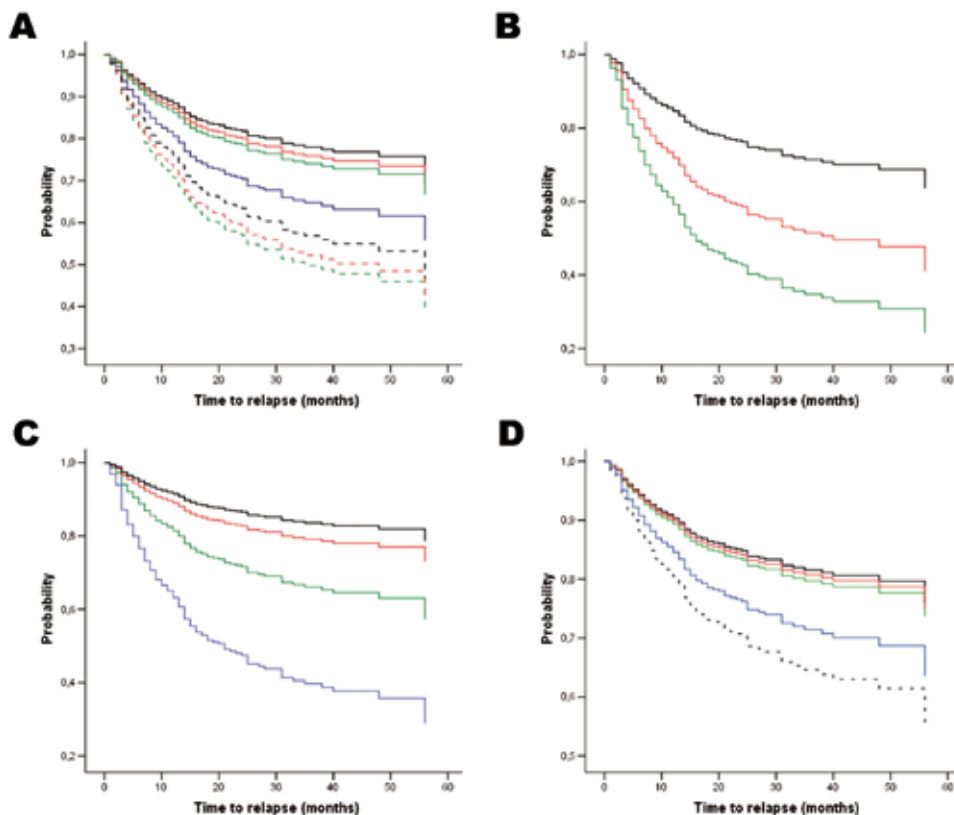


Fig. 1. Five-year risk of relapse after the treatment of primary basal cell carcinoma (BCC). The treatment outcome of 1139 histologically verified BCCs were analysed by forward Cox regression. (A) Effect of tumour localization (trunk: black, lower extremities: red, neck: green, central face and ears: blue, upper extremities: stippled black, lateral face: stippled red, scalp: stippled green). (B) Effect of T-stage (tumour size) (T1: black, T2: red, T3: green). (C) Influence of treatment modality (excision: black, radiotherapy: red, curettage: green, photodynamic therapy: blue). (D) Effect of concurrent diseases (organ transplant recipients: black, chronic inflammatory skin disease: red, immunosuppressed patients (patients with HIV infection or leukaemia; excluding organ transplant recipients): green, extracutaneous tumours: blue).

PDT had significantly higher recurrence rate (OR 2.3 (CI 0.9–2.0) and OR 5.2 (CI 3.5–7.5), respectively) (Fig. 1C). Unexpectedly, we found that the patients suffering from a chronic inflammatory skin disease (psoriasis, atopic dermatitis, eczema) ($n=125$) and the immunosuppressed individuals ($n=64$) had an approximately 50% lower relapse rate than the healthy patients (OR 0.5, CI 0.3–0.8) (Fig. 1D).

Recurrence rate of primary BCC of the head

Since BCC occurs mostly in the cephalic region and poses a special therapeutic problem, we undertook the separate analysis of risk factors in this group of patients. A total of 534 patients with 601 tumours (385 central face (chin, nose, lips, eye surroundings and forehead) and ears, 162 lateral face (cheeks, temples) and 54 at the scalp) were included. The risk factors resembled those of the primary BCC elsewhere (Fig. 2A). The differences were the significantly higher relapse rate in patients with multiple tumours (OR 1.6, CI 1.1–2.5) (Fig. 2B). The specific localization in the lateral vs. central portion of the face was not a significant parameter for recurrence. Excision seemed to be a slightly better treatment modality than radiotherapy (Fig. 2C), however the statistical significance has not been attain-

ed due to a low number of patients where excision had been performed ($n=26$). As in the unselected primary tumours, curettage yielded a greater than three-fold increase in recurrence (OR 3.5), whereas PDT was associated with a five-fold increase in recurrence rate (OR 5.3, CI 3.1–9.1).

Treatment of relapsing tumours

For the analysis of relapse rates after treatment of recurrent tumours, the data were pooled from the patients who recurred after the treatment at our institution ($n=709$) and those patients who were referred to us from the private practice ($n=381$). The overall relapse rate of the recurrent tumours was approximately twice as high as for the primary BCC (OR 1.8, CI 1.4–2.2), and the facial tumours (OR 2.1, CI 1.4–3.1). The results of single treatment modalities are shown in Fig. 3.

Relapse rates for the patients treated in a specialized skin cancer unit

Relapse rates were compared for the patients treated in a skin cancer unit and those treated in the general dermatology outpatient clinic in our institution. This analysis showed the significant therapeutic advantage

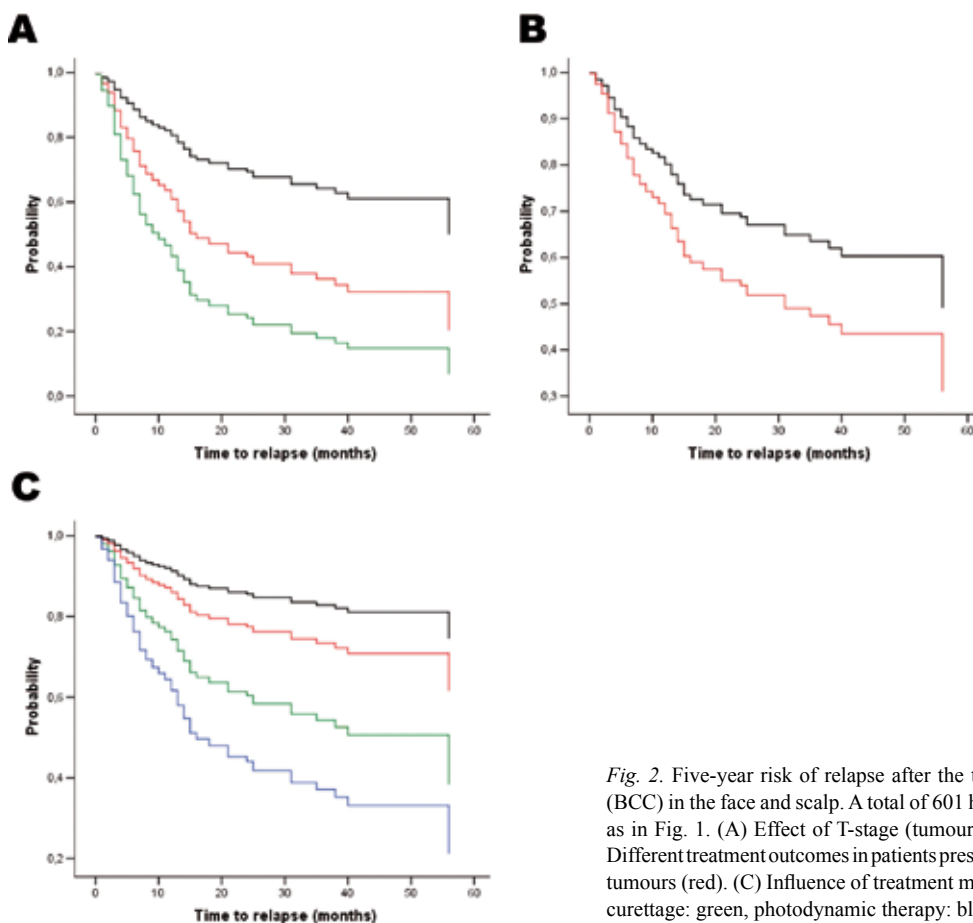


Fig. 2. Five-year risk of relapse after the treatment of primary basal cell carcinoma (BCC) in the face and scalp. A total of 601 histologically verified BCCs were analysed as in Fig. 1. (A) Effect of T-stage (tumour size) (T1: black, T2: red, T3: green). (B) Different treatment outcomes in patients presenting with single BCCs (black) vs. multiple tumours (red). (C) Influence of treatment modality (radiotherapy: red, excision: black, curettage: green, photodynamic therapy: blue).

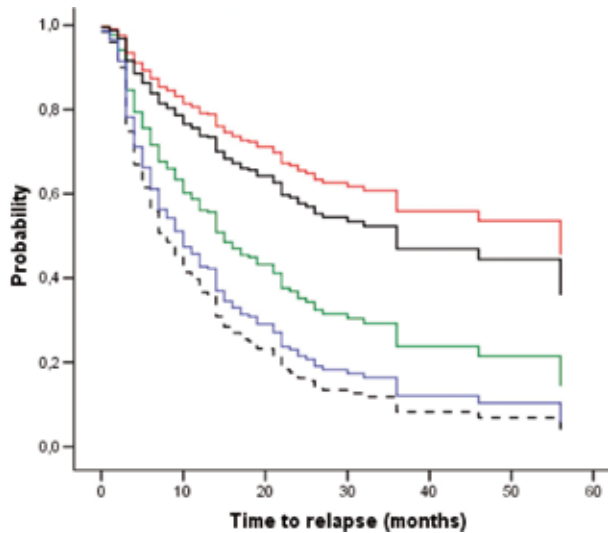


Fig. 3. Five-year risk of relapse after the treatment of recurrent basal cell carcinoma (BCC). Treatment outcome of 1090 recurrent BCCs was analysed as in Fig. 1. Radiotherapy: red, excision: black, curettage: green, photodynamic therapy: blue, cryotherapy: stippled black.

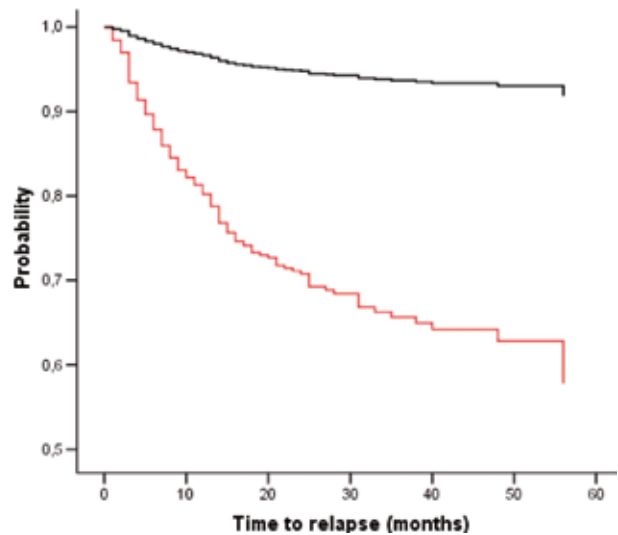


Fig. 4. Risk of relapse after treatment of basal cell carcinoma (BCC) in a specialized skin cancer unit (black line) vs. the treatment in a general dermatology outpatient ward (red line). Cox regression adjusted significant variables (T-stage, localization, concurrent disease, treatment modality).

of the specialized unit (relapse rate 6.4-fold lower, CI 2.4–17.4), when adjusted for the known significant parameters comprising the type of treatment, localization of the tumour, and T-stage (Fig. 4).

DISCUSSION

The drawback of this study is the possible error resulting from the lack of prospective randomization. However, we were able to identify the risk factors influencing treatment outcome in a real life situation. We confirmed that the risk of recurrence depends on tumour size, localization, choice of treatment modality and the clinical experience of the treating physician. Primary T2 tumours relapse twice as frequently and T3 tumours three times as frequently as T1 tumours. BCCs in the head region were more difficult to treat than the tumours on the trunk and lower extremities. However, we could not confirm the data from other studies suggesting that the highest relapse rate occurs after the treatment of BCC in the central face and ears vs. the lateral portions of the face. In our analysis the highest recurrence rate occurred for the tumours on the scalp and, surprisingly, on the upper extremities. Another unexpected finding was that the tumours arising in the context of other skin diseases (such as eczema or psoriasis) or general immunosuppression were characterized by better cure rates than those in otherwise healthy individuals. The role of immunosuppression in the pathogenesis of BCC is well established and it is considered that the tumours in immunosuppressed patients are more difficult to treat (4, 18). The surprisingly good treatment results in this patient group may be explained by an easier access to dermatological care providers and thus earlier diagnosis.

Surgical excision and radiotherapy were the modalities associated with the lowest recurrence rates. In accordance with other results (19) the failure rate of radiotherapy was slightly higher (OR 1.3) than that of surgery, both in unselected BCC tumours and the tumours on the head. The 5-year recurrence rate has been reported to be in the range 15–20% (20), which was also the value obtained in this study. Thus, radiotherapy can be considered as a simpler alternative for the treatment of BCC, especially in elderly individuals where the long-term cosmetic outcome is of a lesser concern than in younger subjects (21). The results also show that radiotherapy could be the preferred option for recurrent tumours, providing comparable, if not better, results than simple excision, with an approximately 60% 5-year cure rate.

Curettage is the most common treatment modality in Europe, but the results are highly variable. In skilled hands curettage can approach the efficacy of surgical excision (1, 15, 22), with cure rate of 90% or higher. However, for the inexperienced physicians the recurrence rates of over 30% are not uncommon, due to a poor curettage technique or inappropriate selection of patients (15, 17, 23). Supervision and more intensive teaching of dermatology residents results in a much lower recurrence rates (23) which is supported here by the data showing a greater than 6-fold decrease in relapses where the BCC were treated in a setting of a specialized skin cancer unit in our institution. Curettage does not seem to be an appropriate modality for the treatment of recurrent tumours and poses a high risk of relapse.

In our centre the efficacy of cryotherapy and PDT were comparable, but significantly inferior to excision, curettage or radiotherapy for unselected tumours and for head tumours. In particular, attempts to treat re-

lapsing BCC with these modalities resulted in only an approximately 20% 5-year cure rate. PDT is a relatively new mode of treatment for non-melanoma skin cancer and actinic keratoses, showing efficacy similar to that of cryosurgery of BCC (24). Several studies reported high cure rates for PDT, ranging from 87% to 53% (1, 25). The cure rate may be increased to 89% by performing the curettage prior to PDT (26). In this study we included the tumours that have not been cured before PDT, which may partially explain the poor results of this treatment modality. It is however unknown at present whether PDT offers any additional benefit over a careful curettage alone.

The results from this study may help further to refine treatment guidelines for BCC and have already led to the establishment of the skin cancer unit at our institution. The high-risk BCC comprising larger than T1 tumours localized on the face or scalp should preferably be treated with excision or radiotherapy. The primary goal is the achievement of complete remission, since treatment of relapsing tumours is associated with a very poor outcome. PDT should primarily be used for small tumours in the cosmetically important areas and its use for relapsing BCC cannot be recommended. The data do not support the use of curettage for the treatment of relapsing tumours. The results of this study also show that the treatment of BCC is still an area of a significant medical need, requiring novel therapeutic modalities providing higher cure rates at less expense.

Conflict of interest: None to declare

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