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Facial Basal Cell Carcinomas Recurring after Photodynamic Therapy: A Retrospective Analysis of Histological Subtypes

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Key Words
Facial basal cell carcinoma · Photodynamic therapy · Histological subtypes · Recurrence · Retrospective analysis

Abstract
Background: Photodynamic therapy (PDT) is an established treatment for basal cell carcinomas (BCCs). Although recurrences are sometime observed, their histological patterns have never been specifically studied or compared with the one of the initial tumor. ***Objective:*** To compare the histopathological aggressiveness of BCCs recurring after PDT with that of the primary tumors. ***Methods:*** The study population included 12 patients with 16 post PDT recurrent BCCs. Outcome measures were proportion of histologically aggressive subtypes in BCC recurrences vs. primary tumor. ***Results:*** 62.5% of recurrent BCCs displayed a transition from a non-aggressive to an aggressive subtype. ***Conclusions:*** Post PDT recurrences appear to display an increased histological aggressiveness, although the latter may reflect the natural course of tumor progression. Despite the presence of potential biases, our study raises the possibility that PDT favors the selection of more aggressive tumor cells. Better systematic large-scale follow-up studies are required to assess the exact frequency and histological types of BCC recurrences after PDT.

Introduction

The incidence of non-melanoma skin cancers is dramatically increasing in all industrialized countries, with basal cell carcinomas (BCCs) accounting for 80% of them [1]. The gold standard treatment remains histologically controlled surgical excision; Mohs surgery is indicated in BCCs with a high risk of recurrence [2–4]. However, since additional BCCs develop in up to one third of patients, especially on the face, multiple repeated excisions are often necessary and require increasingly complex reconstructions [2–4]. In the last decade, huge efforts have been made to develop 'surgery-sparing' procedures, with the ultimate goal of obtaining tumor remission with minimal scarring and of avoiding repeated interventions. Photodynamic therapy (PDT) is one of these alternatives. It combines the topical application of a photosensitizer on the tumor, such as methyl aminolevulinate (MAL), followed by a standardized exposure to visible light. MAL-PDT efficacy is proven for cutaneous superficial premalignant and malignant conditions such as actinic keratosis, Bowen's disease and BCCs

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[5]. Aggressive BCCs (morpheic, micronodular, infiltrating or basosquamous BCCs) are not recognized indications for PDT.

For BCCs, the primary endpoint of most clinical studies has been the complete response rate [6–10]. However, no study has focused on those BCCs recurring after PDT. The changes in histological pattern between the pretreatment tumor and its subsequent recurrence have never been specifically assessed. This knowledge is essential to properly understand the value of PDT and to better delineate its indications. As a first step to study the behavior of post PDT BCC recurrences, we compared the histological patterns of the primary tumor (obtained from pre-MAL-PDT biopsy samples) to those of their recurrences (obtained from surgical excision specimens). Our main objective was to assess the proportion of histologically aggressive BCCs that develop after MAL-PDT.

Table 1. Characteristics of the study population

Patient No.	BCC location	Sex	Age, years
1	temporal	F	67
2	nose	F	61
3	frontal frontal frontal	M	82
4	temporal	M	58
5	nose	F	49
6	nose	M	64
7	frontal	F	67
8	frontal	F	63
9	cheek	M	69
10	temporal nose	M	77
11	temporal	F	65
12	frontal frontal	M	77

Patients and Methods

Population

We retrospectively analyzed all cases of biopsy-proven BCC recurrences following MAL-PDT (January 2008 to November 2010). Patients were included if they presented (1) one or several biopsy-proven BCC(s) on the site(s) previously exposed to MAL-PDT and (2) further histology-proven recurrence. All but one patient (managed by A.S.) were recruited and followed in the Department of Dermatology of the University Hospital of Berne, Switzerland. The following information was obtained from patients' files (table 1): age, sex and location(s) of the tumor(s). For each BCC, we collected (1) the results of light microscopy studies from the pretherapeutic biopsy specimen, (2) the number of MAL-PDT cycles, (3) the time interval between PDT and tumor recurrence, (4) the result of light microscopy studies from biopsy specimen of BCC recurrence, and (5) the definite histopathological findings of the completely excised BCC (table 2). All histological results were re-evaluated independently by a trained dermatopathologist (H.N.).

PDT Procedure and Follow-Up

The PDT was performed twice separated by at least 1 week for both superficial and nodular BCCs and conducted according to the MAL label (Metvix®, Galderma, Switzerland). Nodular BCCs were initially debulked. The 160 mg/g MAL cream was applied approximately 1 mm thick on the lesion and on 10 mm on the surrounding skin, followed by occlusion during 3 h (e.g. Tegaderm®, 3M). The cream was gently cleaned before red light illumination (630 nm) with a noncoherent light source (Aktilite CL128) at an intensity of 50 mW/cm^2 and with a total dose of 37 J/cm^2 at 50 mm from each lesion. In line with the usual daily practice, the complete response was assessed clinically for all patients within the third month. No systematic biopsy was taken in the absence of suspect lesion. The patients were followed further with a maximum time interval of 6 months between 2 visits.

Surgical Treatment Procedure

Recurring BCCs were first confirmed histopathologically by one or several biopsies sampled from the tumor area displaying the most suspect clinical feature (e.g. scarring or morpheic). All but one patient underwent surgical excision, with a preference for micrographic surgery, which allows a thorough analysis of the whole tumor volume. Patient 3 was considered non-operable and treated with radiotherapy.

Histopathology

All tissue samples obtained from biopsies or classical surgical excisions were fixed in 10% formalin. Serial 8-μm sections were cut and further stained with hematoxylin-eosin. When excised by Mohs micrographic surgery, the tumor specimens were orientated, frozen, cut every 100 μm, mounted on glass slides and stained with hematoxylin-eosin. All specimens were analyzed during the routine procedures and reviewed a posteriori by a single blinded dermatopathologist (H.N.). The different BCC patterns were classified as superficial, nodular, micronodular, morpheic or infiltrating, according to Sexton's classification [11] as well as to the recommendations of the National Comprehensive Cancer Network (www.nccn.org). The following were considered as markers of aggressiveness: micronodular, morpheic and infiltrating patterns, in any part of the tumor, as well as perineural infiltration and/or basosquamous differentiation [11]. For every BCC analyzed, the presence of each of these latter patterns was reported, even if minimal. The transition of a superficial or a nodular BCC to any of these aggressive forms was considered a histological aggravation. Conversely, the recurrence of a superficial BCC into a nodular BCC was not considered an aggravation.

Table 2. Recurrent BCCs: histological findings before and after MAL-PDT

Patient No.	Primary BCC		Recurrent BCC				Evolution
	histology/biopsy	treatment	delay post PDT, months	histology/biopsy	treatment	histology/excision material	
1	superficial	PDT × 2	4	nodular	Mohs	nodular	stabilization
2	superficial	PDT × 2	6	nodular	Mohs[a]	micronodular morpheic infiltrating	aggravation
3	superficial[b]	PDT × 2[c]	11	morpheic infiltrating	radiotherapy	ND	aggravation
	superficial[b]	PDT × 2[c]	11	morpheic infiltrating	radiotherapy	ND	aggravation
	superficial[b]	PDT × 2[c]	11	morpheic infiltrating	radiotherapy	ND	aggravation
4	nodular	PDT × 3	12	nodular	Mohs	nodular micronodular	aggravation
5	nodular	PDT × 2	12	morpheic	Mohs	morpheic	aggravation
6	nodular	PDT × 2	14	nodular	Mohs	nodular	stabilization
7	nodular	PDT × 2	16	nodular	Mohs	nodular	stabilization
8	nodular	PDT × 2	19	ND	SE	nodular	stabilization
9	superficial	PDT × 2	25	nodular	Mohs	basosquamous	aggravation
10	nodular	PDT × 2	26	nodular	Mohs	micronodular	aggravation
	nodular	PDT × 2	26	nodular	Mohs	morpheic micronodular	aggravation
11	nodular	PDT × 2	29	nodular	Mohs	morpheic micronodular	aggravation
12	superficial	PDT × 2	33	superficial	Mohs	nodular	stabilization
	superficial	PDT × 2	33	nodular	Mohs	nodular	stabilization

ND = Not done; SE = conventional surgery.
[a] The patient remained treatment-free 20 months after recurrence. [b] Foci of superficial BCCs observed on resection margins during initial Mohs procedure (complete excisions of 3 primary nodular BCCs). [c] Adjuvant treatment proposed for foci of superficial BCCs, remaining after complete excision of nodular BCCs.

Results

Population Characteristics (table 1)

We included 12 patients presenting with a total of 16 recurrent BCCs. The male/female ratio was 6/6 and the mean age at recurrence was 66.5 years. The locations of the BCCs were: nose (n = 4), frontal area (n = 7), temple (n = 4) and cheek (n = 1). Both ages of the patients and locations of their tumors were in line with those expected in the general BCC population. All patients were initially successfully treated by 2 MAL-PDT cycles.

Delay of BCC Occurrence after the Last PDT Session

The delay of recurrence ranged from 4 to 33 months (mean 14.1 months).

Surgical Treatment

All but 2 patients were operated by Mohs micrographic surgery; 1 underwent conventional surgery with appropriate safety margins (table 2). As already mentioned, patient 3 received radiotherapy. The whole cohort entered into a regular follow-up program.

Pathological Examination (table 2)

Histopathological Patterns of the Primary BCCs. The light microscopy studies of the biopsy specimens obtained from the primary BCCs showed a superficial and a nodular pattern in 8 and 8 cases, respectively. The primary superficial BCCs observed in patient 3 were diagnosed during micrographic surgery of 3 nodular BCCs, where multiple foci of superficial BCCs were in contact with the surgical margins and justified a postoperative adjuvant MAL-PDT [12].

Histopathological Patterns of Recurrences: Biopsy Samples. BCC recurrence was first confirmed on biopsy samples in all but one of the cases (patient 8). For the 8 primary superficial BCCs, the recurrences were assigned as follows: superficial BCC (n = 1), nodular BCC (n = 4) and composite morpheic-infiltrating BCC (n = 3). For the 8 primary nodular BCCs, they were diagnosed as nodular BCC (n = 6) and morpheic BCC (n = 1). For patient 8, no pretreatment biopsy was performed.

Histopathological Patterns of Recurrences: Surgical Resection Samples. The vast majority of BCCs (12/16) were analyzed during the micrographic surgery procedure; only one was assessed using the bread-loaf technique. For

patient 3, the 3 BCC recurrences where proven to be aggressive pattern (i.e. morpheic and infiltrative) on the biopsy specimens obtained prior to radiotherapy. Neither isolated superficial BCCs nor perineural infiltration were observed. BCCs were defined as morpheic if they displayed the classical picture described by Sexton et al. [11]. The subdermal band-forming fibrosis classically induced by PDT could most of the time be easily distinguished from the morpheic pattern, the later extending deeper. The repartition was as follows: nodular (n = 6), micronodular (n = 2), morpheic (n = 1), composite morpheic-micronodular (n = 2), composite morpheic-micronodular-infiltrating (n = 1) and basosquamous (n = 1). Altogether, the occurrence of an aggressive histological subtype was observed in 10/16 (62.5%) BCC recurrences. The 37.5% remaining BCCs showed an unchanged non-aggressive pattern. Additionally, in 12 of the 16 BCCs, we were able to compare the histopathological results obtained from pretherapeutic biopsy specimens to those from complete tumor analysis. Histological aggressiveness was missed by biopsy alone in 50% of cases.

Discussion

This first retrospective histopathological analysis of BCCs recurring after MAL-PDT provides evidence that 62.5% of the superficial or nodular primary BCCs showed a relapse characterized by a more aggressive histological pattern. Although the latter may reflect the natural course of tumor progression, our data suggest that BCCs recurring after PDT show an as yet unrecognized risk of behaving more aggressively.

Several prospective studies have demonstrated the efficacy and safety of MAL-PDT in the treatment of superficial and nodular BCCs [6–10]. Yet, in analogy to other destructive and non-histology-controlled treatments (e.g. radiotherapy, cryotherapy, topical imiquimod), little is known about the histological aggressiveness of tumor recurrences. There are few studies which have analyzed BCCs recurring after surgery. Menn et al. [13] described a 'change from solid nests of tumor cells within mucinous stroma to infiltrating elements embedded in a dense connective stroma tissue'. By the same histopathological criteria used in our study, Boulinguez et al. [14] described aggressive recurrences in 4 of 20 (20%) superficial or nodular BCCs. Lang and Maize [15] also observed an increased aggressiveness in 23.5% of 51 recurrent BCCs.

The 62.5% histopathological aggravation rate observed in our group is much higher than that observed with conventional surgery. Can this figure be artificially overestimated? A first bias could be related to the elective referring of more severe recurrences to our University Hospital. This seems very unlikely since the patients were primarily treated by PDT in our center. One may also question the high proportion of superficial facial BCCs (50%, see table 2) which is inconsistent with their relative scarcity in this topography (around 6% in the study of Scrivener et al. [16]). We interpret it as a treatment selection bias, PDT being encouraged for this subtype of tumor. Finally, another source of errors is the questionable reliability of the initial biopsy examination. The latter can in fact miss the more aggressive component of a composite BCC in more than 40% of cases [11, 17, 18]. Composite aggressive and non-aggressive BCCs have been detected in 38.5% of a series of 1,039 cases [11]. Cohen et al. [19] studied the slides obtained from 144 Mohs surgery excisions and found a mixed histology in 43% of cases. Strikingly, this mixed pattern was found in only 10% of the initial preoperative biopsies. In this scenario, it is conceivable that MAL-PDT will only destroy the nodular or superficial component, leaving intact remnants of aggressive BCC. The latter may then explain the apparent increased histological aggressiveness of the recurrent lesions.

The scarring process associated with PDT likely makes the recognition of partial responses and/or recurrences clinically more difficult. PDT induces a dense sclerosis involving the superficial dermis with a sharp lateral delimitation [20]. The same has been observed in our BCC recurrences, in which tumor cells extended both more laterally and deeper than this homogeneous scarring area. Additionally, as described after curettage or electrodessication, tumor nests of resistant or undertreated cells could persist and initiate multifocal recurrences [21]. When Mohs surgery [2, 4, 22] is chosen for treating these cases, the potential lack of tumor continuity makes the three-dimensional reconstruction of the tumor volume very delicate and the assessment of surgical margins less reliable. In these cases, the new available skin imaging technologies may be useful to better define the surgical margins [23].

Could PDT directly act on selecting or inducing more aggressive tumor cells? Topical PDT has only been anecdotally suspected to induce skin tumors such as melanomas [24] or keratoacanthomas [25]. In vitro and in vivo studies did not provide evidence for any carcinogenic effect on skin: both systemic and topical PDT with aminolevulinic acid delayed the occurrence of UV-induced squamous cell carcinoma in mice [26, 27]. Preventive repeated MAL-PDTs have a protective effect against UV-

induced tumors [28]. However, an extrapolation to human BCCs cannot be made. MAL-PDT induces the production of reactive oxygen species, a key factor for the destruction of target cells, but is also a known inducer of DNA breakages [29, 30]. Some BCC cells that have received a sublethal dose of PDT could accumulate enough DNA damage to behave more aggressively. Alternatively, distinct BCC cells may carry pre-existing genetic alterations making them resistant to PDT-induced apoptosis. The observation that apparently undamaged surviving cells persist after PDT is compatible with this hypothesis [31]. Pre-existing mutations of H-Ras in a subset of tumor cells confer resistance to PDT, as observed in mouse keratinocytes [32].

In conclusion, our work raises the concern that BCCs recurring after PDT show a more aggressive behavior, resulting in more complex surgical interventions. Since aggressive BCCs mostly occur on the face [15], where surgery of recurrences is delicate, we recommend more caution in using PDT for BCCs in this location. Our preliminary findings indicate the need of large-scale follow-up studies to assess the exact frequency and types of relapses of BCC occurring after PDT.

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Disclosure Statement

The authors declare no relevant financial interests.

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