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Gold Standard for Skin Cancer Treatment: Surgery (Mohs) or Microscopic Molecular-Cellular Therapy (Curaderm)?

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Abstract

Non-melanoma skin cancers or keratinocyte cancers such as basal cell carcinoma and squamous cell carcinoma make up approximately 80% and 20% respectively, of skin cancers with the 6 million people that are treated annually in the United States. 1 in 5 Americans and 2 in 3 Australians develop skin cancer by the age of 70 years and in Australia it is the most expensive, amassing $1.5 billion, to treat cancers. Non-melanoma skin cancers are often self-detected and are usually removed by various means in doctors' surgeries. Mohs micrographic surgery is acclaimed to be the gold standard for the treatment of skin cancer. However, a novel microscopic molecular-cellular non-invasive topical therapy described in this article, challenges the status of Mohs procedure for being the acclaimed gold standard.

Keywords

Skin Cancer, Basal Cell Carcinoma, Squamous Cell Carcinoma, Mohs Surgery, Microscopic Molecular-Cellular, Curaderm, Actinic Keratosis, Cosmesis

1. Introduction

Each year in the United States alone, almost 6 million people are treated for skin cancer [1], and the number of new cases is growing [2].

The most common types of skin cancer-basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), known as nonmelanoma skin cancers, are usually treatable, but treatment is expensive and can leave scars.

Early detection and prevention are crucial, but when skin cancer does develop, choosing the right treatment method is imperative.

2. Surgery and Skin Cancer

Surgery is a medical specialty that uses manual and/or instrumental techniques with a knife to physically reach into the skin to treat pathological conditions. This type of approach has been adapted to excisional surgery for treating non-melanoma and melanoma skin cancers. The objective of surgery of skin cancer aims to remove all the skin cancer and leave as much healthy skin tissue as possible.

2.1. Excisional Surgery

Surgery to remove the cancer (standard surgical excision) is one of the most common treatments for nonmelanoma skin cancer. After local anaesthesia the affected area of skin cancer is cut out with some nearby normal-looking tissue (margin). The recommended margin is usually between 2 mm and 10 mm depending on the type and location of the skin cancer. Dermatopathologists check the margin for cancer cells under a microscope to ensure that the cancer has been completely removed. It takes about a week to obtain the pathologist's report. If cancer cells are found at the margin, further surgery or radiation therapy is required. Post-surgery, the resultant wound is stitched, but most likely requires reconstruction with a skin flap, where neighbouring tissue is moved into the wound, or possibly a skin graft whereby skin is transplanted from a distant location to the wound [3].

Traditional excision does not examine the complete margins, which creates an increased risk of false negative margins. Another main disadvantage of the excision and repair of skin cancers is that the excision is operator-dependent and that scarring occurs after the procedure, especially for larger incisions. This procedure also calls for the removal of a relatively large proportion of healthy skin around the tumor, which makes it difficult to put the edges of the resulting wound back together. Standard excision might also necessitate multiple visits and demands specialized expertise and might be time-intensive.

Because of the limitations of excisional surgery for nonmelanoma skin cancer, improvements of this procedure have been developed and have led to Mohs surgery.

Mohs Surgery

Mohs surgery was developed in 1938 by a general surgeon, Frederic Mohs. It began as a technique called chemosurgery. In the mid 1960s, Perry Robins, MD, further developed the procedure with dermatologists and is now known as Mohs surgery, sometimes called Mohs micrographic surgery, that is considered the most effective technique for treating many BCCs and SCCs, the two most common types of skin cancer. Compared to standard excisional surgery, Mohs surgery is a more tissue sparing, precise method of skin cancer removal and offers high cure rates for the treatment of a variety of skin cancers, including BCC and SCC.

Mohs surgery is currently performed by doctors who are especially trained to

fulfil the roles of a surgeon who removes the cancerous tissue and closes or reconstructs the wound and a pathologist who analyses the laboratory specimens.

After local anaesthesia, the surgeon removes a thin layer of visible cancerous tissue. However, some skin cancers may have extensions that are not visible from the surface. Therefore, the surgeon removes another layer of skin. After each removal, the tissue is examined for cancer cells. If any cancer cells remain, the entire process is repeated as many times as needed until there are no more cancer cells.

Depending on the size and location of the surgically removed lesion the resultant wound may be left open to heal or the surgeon may close it with stitches. More often, the wound may need reconstruction with a skin flap, or possibly, a skin graft.

Mohs technique is hailed as a tissue sparing surgical procedure used to remove skin cancers with a high risk of recurrence and located in areas of functional and aesthetic importance.

Compared to standard surgical excision, Mohs micrographic surgery offers 100% margin assessment, same day pathology reports, and single-session removal. In contrast, standard excision may require multiple visits for re-excision and typically provides pathology reports in 1 - 2 weeks. Furthermore, reportedly, Mohs procedure conserves more healthy tissue with higher cure rates, less scarring, lower recurrence rates with improved cosmetic results and is considered the most effective technique for treating BCC and SCC [3].

Although Mohs surgery is microscopically controlled, it is reliant on the assessment of humans; the surgeon, the pathologist and ancillary staff, who seek cancer at a cellular level.

3. Curaderm Topical Cream

In 1987, Bill Cham PhD, reported that plant derived glycoalkaloids solasodine glycosides, including solamargine, solasonine, mono- and di-glycosides of solasodine, known as BEC [4] [5], induced remarkable anticancer effects with high therapeutic indices in cell culture [6] [7], animals [8], and humans [7] [9] [10].

Since then, a plethora of further investigations have resulted in the placement of BEC and its individual components as very promising antineoplastic agents with vast potential to serve as targeted anticancer agents [7]. With BEC, solamargine accounts for 86% antineoplastic activity and solasonine accounts for 9%, whereas the mono- and di-glycosides of solasodine contribute 5% for antineoplastic activity. The anticancer activity of these glycoalkaloids is considered to be concerted and additive [11].

The governing critical principle that determines the potency of antineoplastic activityof BEC is the plant sugar rhamnose that forms part of glycoalkaloid molecule [12]. By way of the rhamnose moiety, BEC recognizes and targets specific mutant endocytic endogenous lectin proteins located on cancer cell membranes that act as specific receptors for these glycoalkaloids. Normal non-cancer cells do not possess such specific receptors and are not affected by BEC.

After binding to these characterised specific receptors [7] [13] [14], BEC is internalised by cell-receptor-mediated endocytosis. This is followed by the anticancer action of solasodine, the other moiety of the BEC glycoalkaloid, involving identifiable anticancer properties of a variety of biological pathways, including cell survival pathways [15], tumour suppressor pathways [16], lysosomal pathways [17], mitochondrial pathways [18], caspase activation pathways [19], death receptor pathways [20], protein kinase pathways [21], and signal pathways that impede invasion/migration and multidrug resistance [7].

BEC exhibits much higher cytotoxic effects on cancer cells than currently used antineoplastic agents such as vinblastine, vincristine, camptothecin, cisplatin, 5-fluorouracil, gemcitabine, epirubicin, cyclophosphamide, taxol and doxorubicin [7].

Furthermore, the absolute concentrations of these drugs to obtain comparable efficacy as BEC, are in the order of 6 - 40 times higher [7].

Moreover, the therapeutic index is much higher for BEC compared to other antineoplastic agents as shown in cell culture studies and animal studies [7]. The high therapeutic index of BEC translates to high safety margins. BEC is effective against over 20 types of cancers [7] and has curative properties in animals with terminal cancer [6] [7]. With the cell culture and animals studies, as little as 8 mg BEC/kg is required to kill the cancer cells and at this concentration BEC does not adversely affect normal non-cancer cells [8].

In 1987 it was reported that topical application of a cream formulation containing high concentrations of BEC was effective in the treatment of the premalignant lesions actinic keratoses and malignant nonmelanoma skin cancers, BCC and SCC [7] [22] [23] [24].

Optimizing the bioavailability of BEC with skin cancer cells at the concentration of BEC that is in the range of anticancer efficacy studies in cell culture and animals resulted in Curaderm, a very safe and effective treatment for skin cancers [7] [24] [25] [26].

4. Results

Double-blind, vehicle-controlled, randomized, paralleled, group studies and other multi-center clinical studies of Curaderm established that Curaderm, as a topical cream formulation, is a very effective, safe treatment with excellent cosmetic outcomes for actinic keratosis [27] [28] [29], BCC [30] [31] [32], SCC [32] [33] [34] and shows promise for stages 0 to 2 melanoma [35] [36]. Dermatologists, pathologists, oncologists and scientists contributed to various study designs with the Curaderm multicenter studies, ensuring the conclusion of statistical significances of efficacy and safety of Curaderm therapy, with small and very large skin cancer lesions. Clinical studies also showed that in cases whereby other well established treatment methods had failed in efficacy of treating skin cancer, subsequent treatment with Curaderm therapy was successful [30] [31].

In 2018 Curaderm was registered as a medical device class 1 by the Decentral-

ised European Authorisation Member State Mutual Recognition Procedure, for the indication "Topical treatment with keratolytic action, and antineoplastic activity in the treatment and healing of basal cell carcinoma of the skin".

BEC in Curaderm are amphiphilic molecules that possess both hydrophilic and hydrophobic properties. The hydrophilic moiety, essentially the plant sugar rhamnose, binds to a mutant protein on malignant cancer cells (**Figure 1**). There are two types of binding of BEC on cancer cells, which are related to receptor affinity and numbers of receptors per cell [7]. Normal non-cancer cells do not contain the mutant protein receptors (**Figure 2**, **Figure 3**).

After binding and internalisation of BEC into cancer cells, the hydrophobic alkaloidal moiety, solasodine, triggers the cancer cell to commit suicide by the process of apoptosis (**Figures 4-7**) [24].

BEC in Curaderm is very specific and effective for cancer cells. **Figure 8** shows that BEC even distinguishes primary and metastatic cancer cells from benign and normal cells.

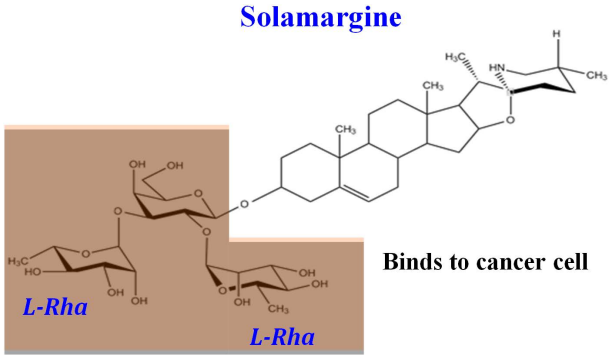
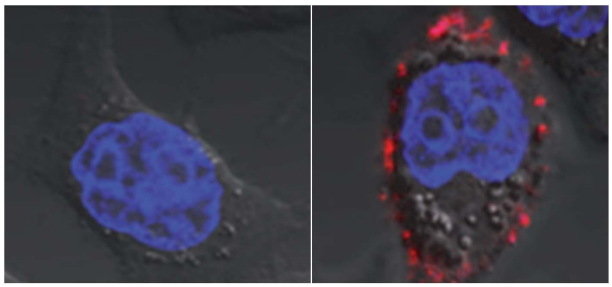


Figure 1. Chemical structure of solamargine, the main anticancer ingredient in Curaderm. The rhamnose sugar moiety (highlighted area) selectively recognizes and interacts with specific mutant rhamnose binding lectin proteins (RBP) that have been identified, characterised and are located on the surface of cancer cells [24].



Normal Cell Cancer Cell

Figure 2. Identification of specific mutant rhamnose binding lectin protein (RBP) receptors on cancer cells by a fluorescence rhamnose probe. Normal non-cancer cells do not possess the RBP receptors. The red images indicate the binding of rhamnose conjugates (solamargine) to RBP receptors [24] [37].

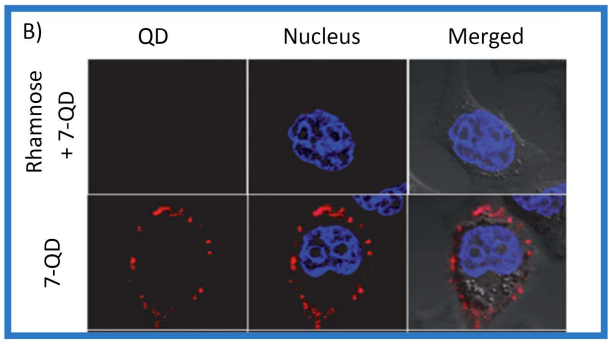


Figure 3. Confocal microscopic view of rhamnose-QD probe (representing solamargine) localized on the cell surface of human squamous cell carcinoma (KB) cells. The binding of the probe is blocked by unbound (free) rhamnose. Confocal microscope image of KB cells labelled by probe (red) and Hoechst stain (blue) [24].

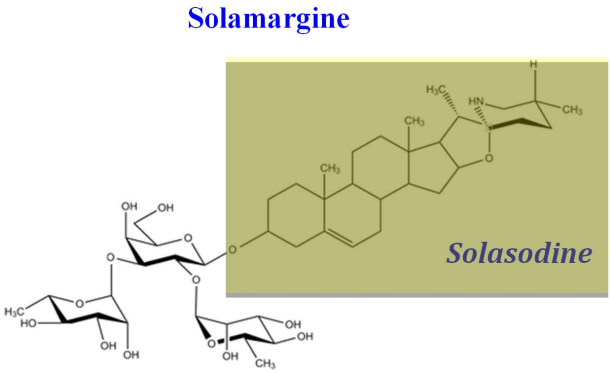


Figure 4. After specific internalisation of solamargine (SM) by receptor-mediated endocytosis into the cancer cell, the alkaloid moiety solasodine (highlighted area) exerts apoptosis in the cancer cell [7].

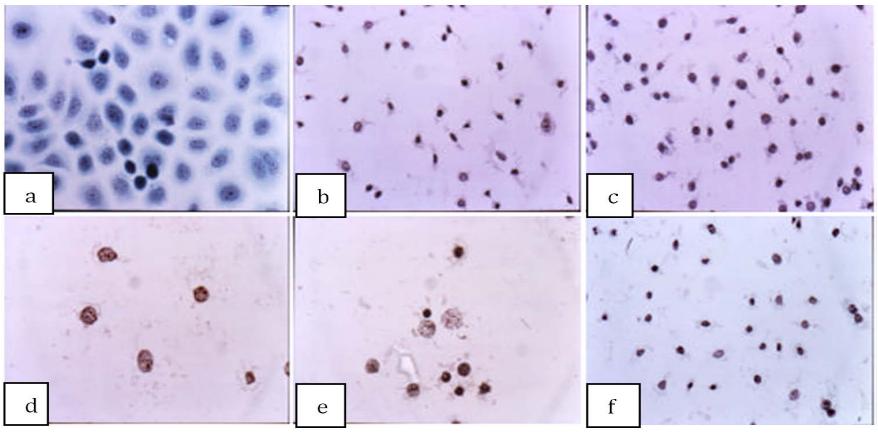
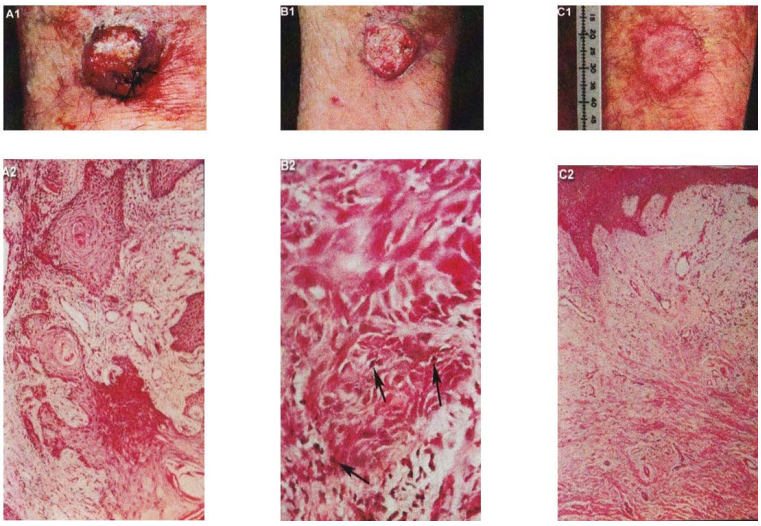


Figure 5. Untreated cancer cells, the cells are all viable (a). BEC causes the cytoplasm of the cancer cells to undergo dissolution, the nuclei contract and become dark staining (b), nuclei then enlarge (c), the chromatin (contents of nucleus) clumps (d) and finally the nuclei disintegrate (e). Only cellular debris is left after the interaction of the cancer cells with BEC (f). This cell death is characteristic of apoptosis, which is also known as programmed cell death [7].



(a) (b) (c)

Figure 6. Clinical and histological diagnosis of an SCC on a leg of a patient before treatment (lane a), during therapy (lane b) and site of treated SCC after completion of therapy (lane c). 1. Clinical diagnosis. 2. Histological diagnosis. Arrows indicate cancer cells dying during Curaderm treatment (lane B2). The observation of this type of cell death caused by Curaderm is similar to those obtained in cell culture studies [7] as shown in **Figure 5**.

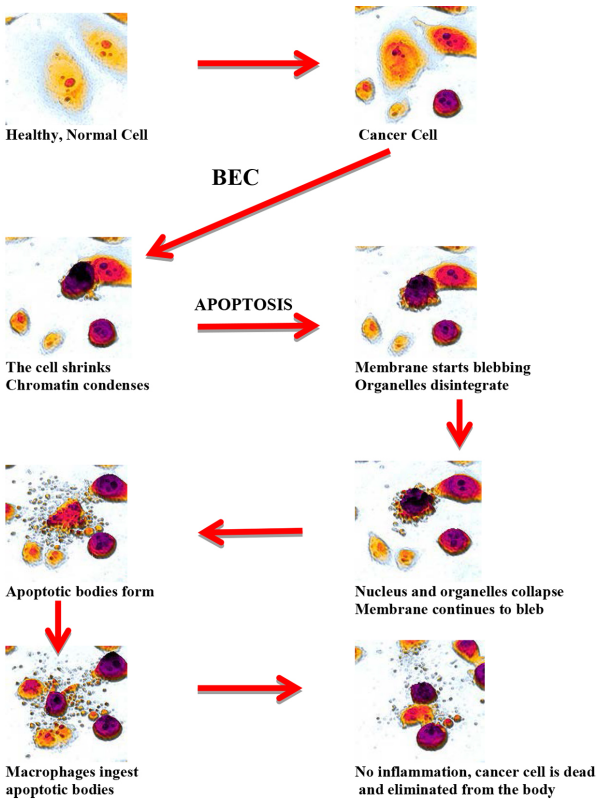


Figure 7. Schematic representation of solamargine (SM)-induced apoptosis by identifiable anti cancer properties through a variety of biological pathways in the cancer cell. The cancer cell dies neatly, without damaging its neighbours [24] as shown in **Figure 5** and **Figure 6**.

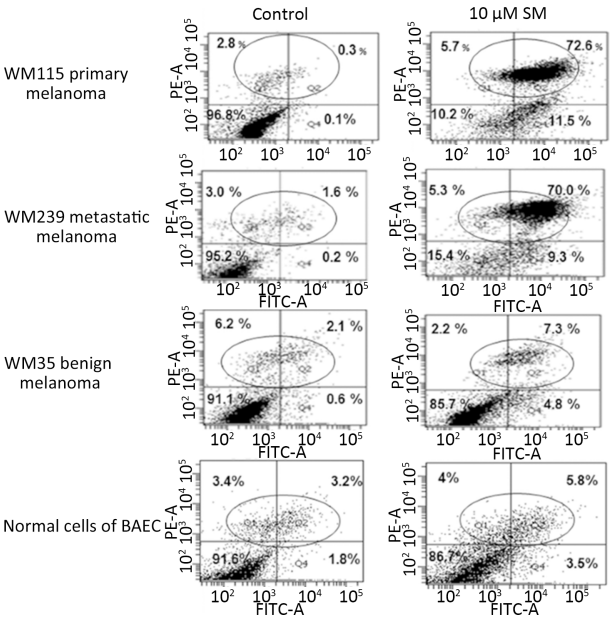


Figure 8. Flow cytometry analysis shows that solamargine (SM) increases cell death tenfold more in malignant to benign cells. 10 μM Solamargine treatment for 2h selectively causes massive cellular death of WM115 primary and WM239 metastatic melanoma cells, which are at least tenfold more than that detected in benign WM35 and/or in aortic endothelial cells (AEC) normal cells. The top right quadrant of the figures indicates cell death. It is seen that solamargine (SM) kills 72.6% of primary melanoma cells and that no treatment kills only 0.3% of these cancer cells (top row). Similarly, SM kills 70% of metastatic melanoma and no treatment kills 1.6% of these cancer cells (second row). Importantly, SM does not significantly kill benign melanoma cells (untreated 2.1%, SM treated 7.3%) (third row), nor does SM kill normal cells (untreated 3.2%, SM treated 5.8%) (fourth row) [24].

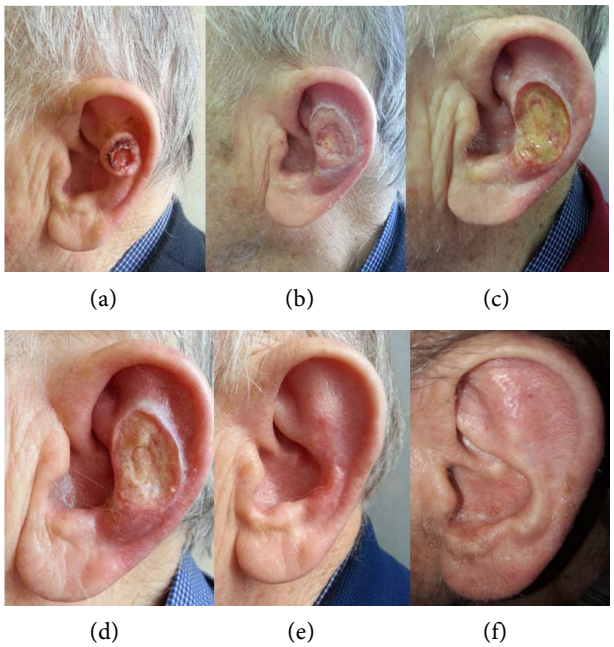
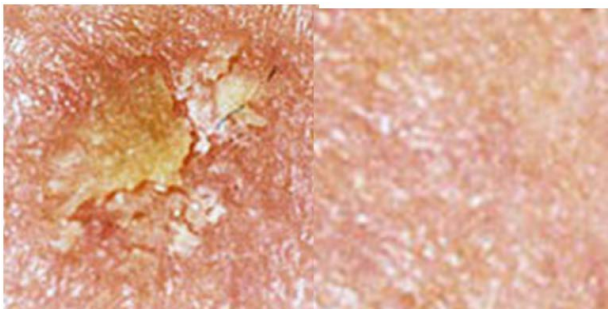


Figure 9. Patient, 85 years. BCC on left ear, before Curaderm pharmacotherapy (a), after 17 days treatment (b), after 28 days treatment (c), after 60 days treatment (d), after 74 days treatment (e). No relapse after 5 years treatment (f) [32].

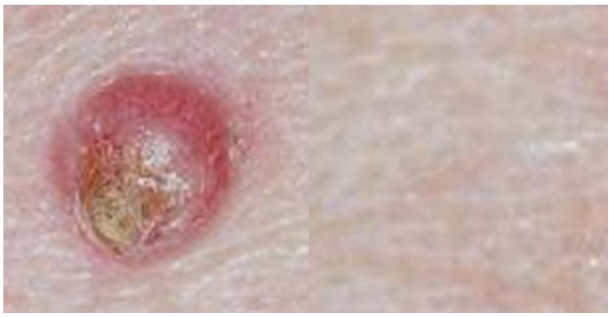
During early elimination of cancer cells with Curaderm, the lesion appears to become larger, followed by the reverse course until the lesion is completely removed and natural self-healing of the treated lesion ensues (**Figure 9**) [30] [32].

Exceptional cosmetic outcomes with Curaderm treatment of various types of skin cancers are remarkable (**Figures 10-13**).



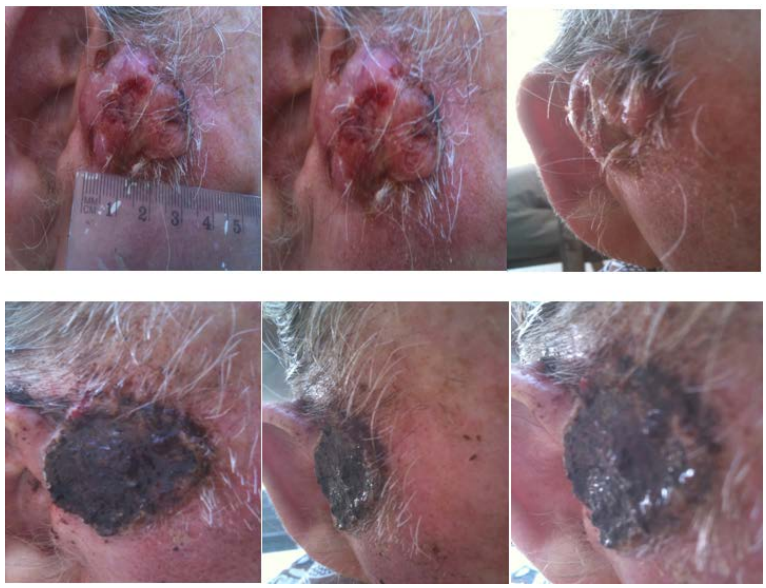
(a) (b)

Figure 10. Actinic Keratosis before Curaderm therapy (a); and 56 days after 3 days of Treatment (b) [7].



(a) (b)

Figure 11. Keratoacanthoma before Curaderm therapy (a); and 60 days after 5 weeks of treatment (b) [7].



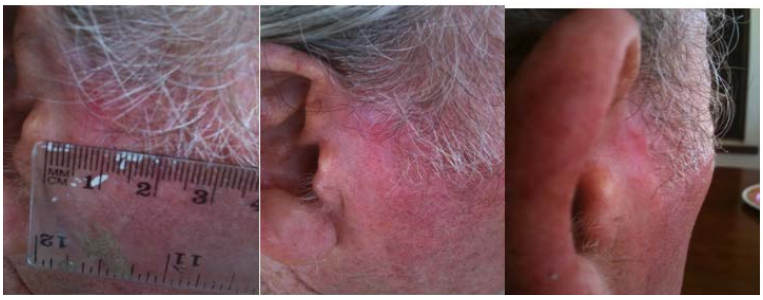


Figure 12. An extensive protruding (4 cm × 4 cm × 2 cm) BCC with central ulceration and raised curly borders on the right side of the face next to the ear is seen in this patient (top row). Treatment with Curaderm resulted in rapid breakdown of the tumour and after 2 weeks of treatment the lesion was reduced to about a half of the original size. Minor bleeding had occurred during this treatment period (middle row). After 14 weeks of treatment the lesion was clinically eliminated. Normal skin cells had replaced the tumour and the cosmetic end result was remarkable, with no scar tissue formation. Even the hairs had regrown where the tumour was originally (bottom row) [32].

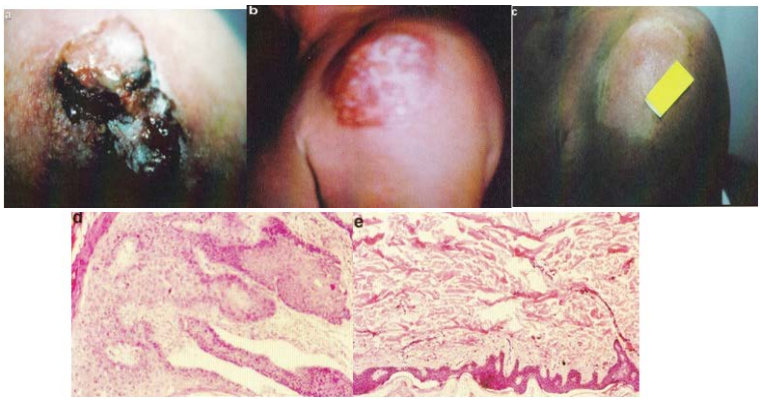


Figure 13. A large SCC (approximately 8 cm × 6 cm) on the shoulder of a patient before (a), during (b) and after (c) treatment with Curaderm. After 10 weeks the tumor was completely healed. The clinical diagnosis was confirmed histologically by punch biopsy (d). After completion of the therapy histopathology determined that no residual cancer was present (e). Clinical assessment 5 years post treatment revealed that there was no recurrence [7].

5. Discussion

In order to understand the important differences between Mohs surgery and microscopic molecular-cellular therapy, comparisons of the two differing procedures are presented in Table 1.

Other important considerations with Mohs and Curaderm therapies

Mohs procedure takes place in an outpatient setting with the surgeon using a local anaesthetic to numb the area completely. The process takes between 4 and 6 hours. Some difficult or larger cases may take even longer. Reported efficacy is over 95% with low recurrence rates.

Table 1. Comparisons of Mohs micrographic surgery to Curaderm therapy.

Mohs	Curaderm
Surgical knife	*Cream*
Invasive	*Topical, effective transdermal delivery*
Necrosis	*Apoptosis*
Experienced operators and ancillary support	*Self-administration*
Anaesthetics	*Occlusive dressing*
Removal of cancer cells and normal tissue	*Removal of cancer cells only*
Skin flaps or grafts or reconstructive surgery	*Natural healing*
Scar tissue	*No scar tissue*
95% success	95% *success*
Low recurrence rates	*Low recurrence rates*
Long waiting time	*No waiting time*
Outpatient, same day treatment	2 *to* 14 *weeks treatment*
Good cosmetic outcome	*Excellent cosmetic outcome*
Expensive	*Economical*

Curaderm is a self-administered home treatment without anaesthetics. Curaderm cream is applied topically twice daily to the lesion with an occlusive dressing. Duration of treatment depends on size, type, and location of skin cancer. Reported efficacy at 8 weeks of treatment is 78% and over 95% at 14 weeks of treatment with low recurrence rates.

Although the duration of treatment by Mohs procedure occurs within one day, this advantage is negated by the long wait time before treatment.

The mean wait time between referral to Mohs treatment is 215.8 days. Importantly, during this long wait time the lesion grows significantly by a factor of 1.41 [38].

There is no wait time with Curaderm. Treatment can start on receiving Curaderm. Indeed, after commencement of Curaderm treatment it takes less time of Curaderm treatment with over 95% efficacy (14 weeks) than the waiting time (30.8 weeks) required for Mohs therapy.

Long waiting times have several deleterious effects. The larger the lesion, the more surgical removal of tissue is necessary with inherent cosmetic sequelae.

The cost of Mohs surgery varies depending on what body part is being treated. The face or scalp can cost between $1.000 - $5.000. Mohs on the hands and feet are usually in the range of $1.200 - $2.800 depending on the complexity of accessing deeper tissues.

The cost of treatment with Curaderm cream is less than 10% when compared with the cost of Mohs surgery.

Because of the modes of actions of surgery or microscopic-molecular-cellular Curaderm therapy, the cosmetic outcomes are very different. Surgery often requires a skin flap or skin graft with consequent scar formation and is dependent on the skill of the surgeon.

The cosmetic outcome with Curaderm is remarkable and is not dependent on

human skill, but on the microscopic interaction of Curaderm with cancer cells.

Mohs surgery necessitates specially trained dermatologists whereas, Curaderm therapy requires only supervision of the treatment by general practitioners, translating to a much wider treatment availability.

Dermatologists should not be wary of a new treatment but should consider it as an addition to their expertise and ameliorate it as a supplementary new tool to complement their acumen and to extend patient care. The health and economic benefits of skin cancer intervention with Curaderm are transparent.

Natural or human intelligence resulted in Curaderm, a treatment for skin cancer. Much information was generated during its development that may, in combination with other treatment procedures, potentially guide to therapeutic applications, resulting in algorithms that may lead to not only diagnosis, but also, treatment of skin cancer by Artificial Intelligence (AI).

6. Conclusions

Excisional surgery aims to remove all the skin cancer cells and to reduce the amount of healthy skin tissue that is removed with the cancer. Although this is achievable, this procedure is considered suboptimal, and is being replaced with Mohs surgery, whereby it is considered that less healthy skin is removed resulting in improved cosmesis. Regardless, with Mohs surgery, skin flap or graft may still be required. These two surgical types of physical procedures result in scar tissue and are completely dependent on the multifaceted skills of the operators. However, although Mohs surgery is an overall improvement of excisional surgery, it falls short in removing **all** the cancer cells without removing **any** normal tissue cells.

With topical Curaderm therapy the specific anticancer action occurs at the microscopic molecular-cellular level without operator intervention, resulting in the **removal of all cancer cells without removing any normal skin tissue**.

Conflict of Interest

Dr. Cham holds patent rights on BEC technology.

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