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A comparative retrospective study of Mohs micrographic surgery and vismodegib chemotherapy for the treatment of advanced basal cell carcinoma

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BOSTON UNIVERSITY

ARAM V. CHOBANIAN AND EDWARD AVEDISIAN SCHOOL OF MEDICINE

Thesis

**A COMPARATIVE RETROSPECTIVE STUDY OF MOHS MICROGRAPHIC
SURGERY AND VISMODEGIB CHEMOTHERAPY FOR THE TREATMENT OF
ADVANCED BASAL CELL CARCINOMA**

by

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B.S., Tufts University, 2020

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ABSTRACT

Basal cell carcinoma is the most common form of human malignancy, and as such there are varied methods for treating its various forms. Its more advanced and aggressive forms have required both the use of and advent of therapies which offer differing safety profiles, cost, and efficacy. Two therapies which differ substantially in these respects but have overlap in their recommended use are Mohs micrographic surgery and the pharmaceutical drug vismodegib. Few studies have sought to compare the two methods using these criteria, and as vismodegib has only received FDA approval in the past ten years, it is worthwhile to explore the limitations and advantages of each therapy. In exploring previous clinical trials and retrospective studies, the two therapies are put side by side to contrast their results with their shared intended use. The general findings were that Mohs micrographic surgery remains the gold standard for the treatment of locally advanced basal cell carcinoma, and there are few demonstrable instances in which vismodegib could be deemed a more appropriate therapy. The future of vismodegib appears to be in its use as a

neoadjuvant therapy for locally advanced basal cell carcinomas for which a decrease in size by vismodegib would allow for better treatment outcomes.

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LIST OF ABBREVIATIONS

AK	Actinic Keratosis
BCC	Basal Cell Carcinoma
ED&C	Electrodessication and Curettage
Hh	Hedgehog
ISO	International Standards Organization
laBCC	Locally Advanced Basal Cell Carcinoma
MBCC	Morpheaform Basal Cell Carcinoma
MMS	Mohs Micrographic Surgery
NMSC	Nonmelanoma Skin Cancer
PCTH1	Patched Homologue 1
SCC	Squamous Cell Carcinoma
SMO	Smoothed Muscle Homologue
QOL	Quality of Life

INTRODUCTION

Basal Cell Carcinoma

Nonmelanoma skin cancer (NMSC), which includes basal cell carcinomas (BCC) and squamous cell carcinomas (SCCs), is increasing in incidence worldwide. As a consequence of a growing aged population and increased sun exposure- BCCs represent the most common human cancer¹.

The causes for basal cell carcinoma are, generally speaking, chronic sun damage (caused by UV rays) and immunosuppression. While typically observed as a malignancy of the elderly, younger patients living in areas with greater sun exposure (i.e. closer to the equator) may also develop BCCs, especially if these patients engage in activities like the use of tanning beds or smoking².

Alternatively, BCCs are observed to more frequently arise in individuals that are immunosuppressed, such as in the case of patients undergoing organ transplantation and thus requiring immunosuppressive drugs, or in patients in immunosuppressive states such as those affected by HIV/AIDS². Further, it has been also shown that BCCs can develop early in life due to genetic (as in the case of genodermatoses) or hereditary factors (albinism). Overall, the lifetime risk of development of BCCs stands at $\geq 20\%$ for the general population and $\geq 30\%$ for whites, with an estimated 2 million occurrences in the United States alone per year³.

Basal cell carcinomas are noted to have several clinical subtypes. The most common forms of these are the nodular basal cell carcinoma, the superficial

basal cell carcinoma, and the morpheaform basal cell carcinoma, in order from most to least common⁴. The nodular BCC accounts for some 50 to 79 percent of all BCCs and is most often noticed due to its stereotypically pearly/shiny appearance and presence of arborizing, or tree-like, telangiectasias⁴ (abnormal dilations of superficial blood vessels just below the surface of the skin⁵). Nodular BCCs are noted for their ability to grow, ulcerate, and bleed when subjected to even *minor* trauma. They have been noted to occur most commonly on the head (more specifically, the cheeks, forehead, eyelids, and nasolabial folds⁴). Worth noting, as in **Figure 1**, is the fact that this form often presents as a papular or *raised* lesion¹. Histopathologically, the nodular subtype consists of a proliferation of basaloid cells which coalesce and sometimes extend into subcutaneous tissues, there is also typically spacing noted between tumor nests and surrounding connective tissue elements⁶.

Figure 1: Nodular Basal Cell Carcinoma, Notable Pearly Appearance, and Prominent Telangiectasias⁷

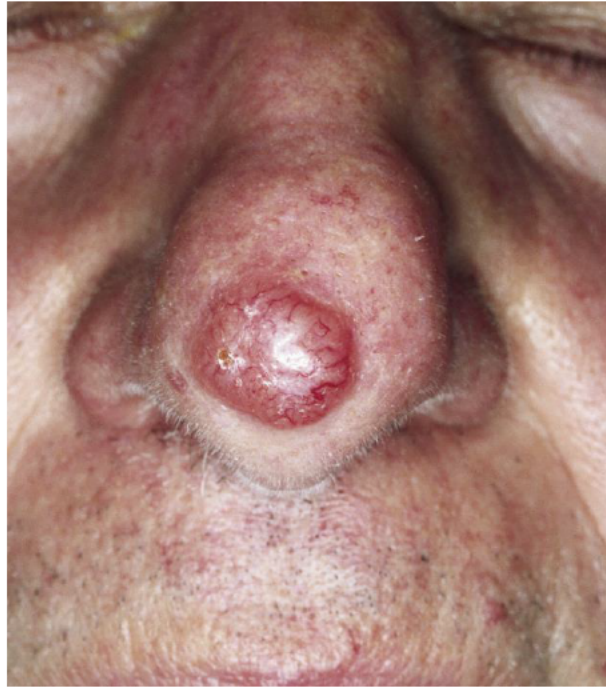


Figure 2: Nodular Basal Cell Carcinoma, H + E Stain, Notable Tumor Nests at Center (Deeply Stained Regions)⁸



Superficial BCCs, which account for approximately 20% of all BCCs, more often occur on the limbs and trunk and are generally notable for having a red, scaly appearance upon initial examination. Closer examination with a dermatoscope may reveal finer details such as short telangiectasias, small erosions, and hyper- and hypo- pigmentation without structure⁶. Histopathologically this subtype is noted for having small islands of basaloid tumors attached just below the epidermis, typically confined to the papillary dermis⁶. Worth noting about this subtype is its typically being *multifocal*, thereby leading to a possibility of an incomplete excision of the lesion¹.

Morpheaform BCC, also known as sclerosing or desmoplastic BCC, is the third most common subtype. It accounts for roughly 10 percent of BCCs, and very closely resembles scar tissue, for which it can be misdiagnosed. Generally this form of BCC is more aggressive than others, and tends to spread subclinically, below the surface of the skin¹. Histologically, the MBCC is notable for its collagenous bordering of narrow, elongated or otherwise smaller islands of tumor cells⁶. The aggressive nature of these lesions will be of note later, as this subtype will be among those most typically termed to be “advanced” due to histological features as opposed to location alone. The subtlety of the morpheaform subtype can be noted in **Figure 3**, where a biopsy proven instance is demonstrated.

Figure 3: Morpheaform Basal Cell Carcinoma with Noted Subtlety⁹



Table 1. The Three Most Common Forms of Basal Cell Carcinoma.¹⁰⁻¹²

Subtype Name	Clinical Features	Histological Features
Nodular	Pearly, arborizing telangiectasias, shiny, rolled borders. Often a papule or nodule. May be ulcerative.	Islands of haphazard cells, with palisading (parallel arrangement) at margins, haphazard at center.
Superficial	Thin, scaly, erythematous plaque. Often has rolled, pearly borders. May resemble eczema or psoriasis. May be ulcerative.	Multiple, small buds of basaloid cells coming down from epidermis with no invasion of dermis.
Morpheaform	Firm, yellow-white, flat	Spiky, thin basaloid

	plaque. Ulceration typically <i>not</i> apparent.	strands that invade dermis. When nests have spiky projections into dermis, this is considered an infiltrative BCC.
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There are, of course, other subtypes of BCC (at least 26 in total), but the most typical are those described above for the sake of generalizing course of treatment and identification¹². As in the case of many skin tumors, a biopsy is necessary to confirm both general diagnosis of a BCC, as well as subtype. Depending upon the location, size, and features of the lesion this biopsy might take the form of a shave or punch biopsy. Between these two biopsy methods there is no apparent notable difference in accuracy, with both having a similar success rate close to 80% in accuracy, though this is merely an estimate from a single clinical trial¹³.

Though very rarely known to metastasize, basal cell carcinoma is treated due to its proving to be destructive to the skin, and sometimes painful to those affected. Given the wide variety of subtypes and locations, as well as the high occurrence rate, the treatment options available are fairly variable. Local treatments, as opposed to more severe methods like chemotherapy, are generally preferred for most instances of BCC, due to their unlikelihood of metastasis¹⁴. A standard surgical excision, within an outpatient setting performed by a dermatologist, is often the first-line treatment for BCCs after initial biopsy and confirmed diagnosis by a dermatopathologist. The cure rate for a standard

excision is typically greater than 95%, with recurrence rates estimated at 3% and 12% over a 2.5 and 10 year period, respectively¹⁴.

Alternatively, for lower risk subtypes like the superficial variant, an ED&C (electrodessication and curettage) might be performed wherein a combination of a curette and cautery is used to destroy the cancerous lesion. Similarly, cryotherapy with liquid nitrogen might be performed for the same purpose of achieving destruction of the lesion, or perhaps a topical chemotherapy like 5-fluorouracil. These aforementioned treatments are often inexpensive and with few side effects, but are consequently more likely to have lower cure-rates¹⁴.

Less common, but more sophisticated and expensive therapies that are used in instances of complex, recurrent, or otherwise more complicated cases are Mohs surgery and hedgehog pathway inhibitors.

Mohs Surgery

While the majority of non-infiltrative BCCs on the trunk and limbs are treated by methods like an ED&C or surgical excision, more challenging areas on the head, neck, genitals, and digits- especially if of an infiltrative type, are better treated by Mohs micrographic surgery (MMS).

MMS has its origins as a form of chemosurgery, wherein a chemical fixative (zinc chloride) is injected directly into a patient's lesion and its peripheral margin. After several hours, the lesion and surrounding tissue are removed readily, from an often bloodless field, permitting the surgeon to then examine the

tissue under microscope directly, with no need for an alternative fixative (e.g., formalin)¹⁵. While a novel approach, this method presents a problem in that these injections are painful, both before and after surgical excision¹⁵.

After determining that his first attempts were unsatisfactory, Dr. Frederic E. Mohs, after whom the surgery is named, began experimenting with cold sectioning. Cold sectioning refers to the practice of freezing tissue specimens, after they have been surgically removed, in order to perform rapid microscopic analysis of tissue- the tissue is first frozen, and then cut with a microtome prior to being stained and placed into a slide for analysis¹⁶. Cold sectioning drastically reduces the time for surgical excisions. It improves upon the lengthiest aspect of simple surgical excision, the time required for fresh tissue to be soaked in chemical fixative.

While standard surgical excisions in dermatology are generally quite quick, there is significant time required for diagnosis to be rendered. Prior to evaluation of a specimen by a dermatopathologist, tissue removed from a patient must be rendered "fixed"- typically with formalin- so that cell and tissue components are preserved for histological evaluation¹⁷. For example, while a surgical encounter might take as little as 30 minutes (wherein local anesthetic is injected, the skin is properly disinfected, the lesion and a margin of healthy tissue are removed and placed into fixative, and the surgical wound is closed with suture¹⁸) the time for fixation prior to later histological preparation can be lengthy depending on the size of the specimen. Fixation is an important component of

the treatment timeline as the surgical specimen must be held in an “arrested” state so that it does not degrade over time. The dermatopathologist examining a removed basal cell carcinoma will have great difficulty in determining the adequacy of removal should the specimen have degraded, with structural components unable to be determined. Without even accounting for later tissue processing, placement of the specimen into wax, microtomy, staining, and histological evaluation- the process of fixation alone has a recommended time of 24 hours (or 1 hour of fixation per 1 mm of specimen) at least in neutral, buffered formalin¹⁹. With frozen tissue these times can be cut down to mere minutes¹⁶.

As a result of using fresh tissue that has been frozen-sectioned, the surgeon is no longer left in the dark as to how much of the lesion actually remains within the patient. As opposed to sticking with a standard guideline, such as a low-risk BCC requiring a 4-5 mm margin of healthy tissue versus a 13-15mm margin in a standard excision, smaller margins can be taken, sparing as much of the patient’s tissue as possible²⁰. This is because the surgeon can take small margins incrementally- so that if additional cancerous tissue remains, it can be excised in additional stages.

By continually removing tissue with lesional involvement, examining the direction in which lesion remains, and finally closing the surgical wound within the same visit the patient was left with a greater cosmetic outcome (being of great importance for lesions affecting the face) while leaving an outpatient surgical setting with the peace of mind that the whole of the lesion has been removed¹⁵.

It is worth noting that Mohs micrographic surgery should not be considered the next “evolution” of the surgical excision. There are certainly instances, as when a lesion is of a less complex or infiltrative subtype where a standard excision would offer a fine outcome, especially when tumors occur in less cosmetically sensitive areas.

Worth noting concerning the differences between surgical technique in a standard excision and Mohs surgery is the general orientation and shape of excised tissue. In the majority of standard excisions on the limbs and trunk the surgeon makes use of an elliptical/fusiform shaped cut. This cut, following fixation, is bread loafed into a series of slices from which slides can be obtained. Unfortunately, these slices may not always be representative of the true depth of the lesion (as demonstrated by **Figure 4**). Further demonstrated by this same example is the fact that though the margins were wide, lesional tissue remained due infiltration into the subcutaneous tissue. The patient from which this tissue has been removed is now likely to experience recurrence later and will need to have this tissue treated again. In the instance of a patient treated with Mohs micrographic surgery, the outcome is far different. In theory they are should be able to walk out of a scheduled surgical visit with their cancer confirmed as having been excised, with a lower likelihood of occurrence.

Figure 4: Standard Fusiform Excision, Notable Incomplete Removal of Lesion. Part A demonstrates first removal of lesion via fusiform excision with small dark spots demonstrating deep infiltration of cancerous tissue. B demonstrates additional cutting (“bread-loafing”) of tissue for histological evaluation. C demonstrates what would be determined upon histological evaluation, that the cancerous tissue appears to have been fully excised, though this is not the case²¹

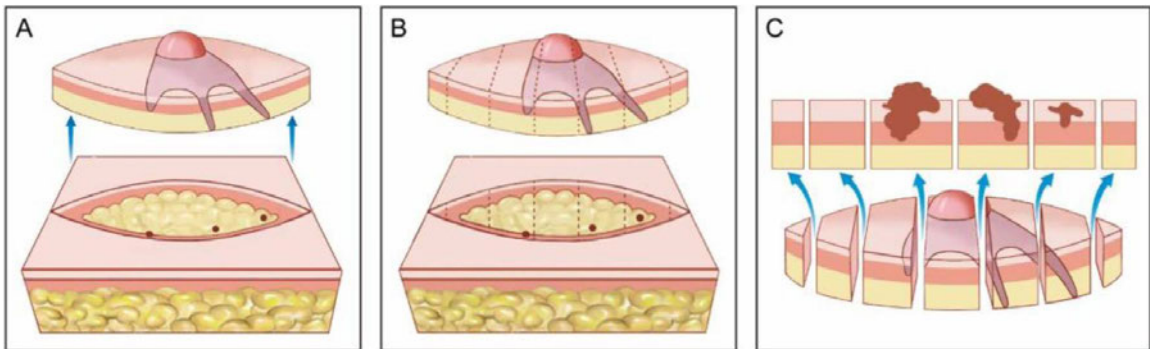
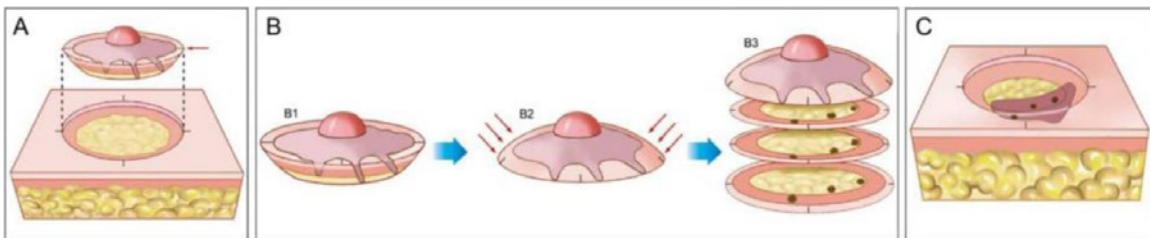


Figure 5: Mohs Micrographic Surgery, Multiple Levels Examined. Blue arrows demonstrate alternative technique of evaluation, the histologist/surgeon will be able to examine the lesion level-by-level.²¹



One can see in **Figure 5** that a typical approach to the excision is a round, saucer-like removal of lesion and perilesional tissue, with margins oriented like a clockface (i.e., 12 o'clock, 3 o'clock, etc.), as demonstrated by the markings on image C. These oriented margins are especially useful to the surgeon in that it allows them to determine which direction the cancerous tissue remains and can make use of the orientation as one might a compass when following a map.

Additionally a smaller margin of healthy tissue is removed, thereby promoting a greater cosmetic outcome²¹. Please note also that as the “roots” of the lesions are noted by surgeon during microscopy, the additional stages of the excisions, should they be required, can focus solely on those areas without the need for a more drastic removal of tissue.

In talking about the cosmetic results of MMS it's worthwhile now to make note of the fact that the responsibilities of the physician performing MMS are multifaceted. The Mohs physician acts both as dermatologic surgeon and dermatopathologist, and then often employs plastic surgery techniques to close what many times are quite large defects. That's not to say that the Mohs surgeon does not make use of consultations for some cases- the most notable and perhaps commonplace of these consultations being that required of a dermatopathologist during a procedure known as “slow Mohs”.

Slow Mohs involves the use of a larger pathology laboratory, wherein the surgeon makes use of a formalin fixative and the specimen is processed over the course of a full 24-48 hours²². This procedure removes a fair amount of the benefit of the Mohs technique in that it may require patient follow-up within a day or so of the first surgery date, but it is a method required of non-superficial forms of melanoma, as well as some infiltrative forms of NMSCs, like BCC^{22,23}. Despite the time added to the procedure by making use of a chemical fixative and the use of an outside laboratory, the conservative approach to the excision is still maintained and benefits the patient.

Overall, Mohs surgery has been demonstrated to be a sophisticated, conservative approach to the removal of skin cancers, and is generally the indicated treatment for complex BCC subtypes and/or lesions on areas where a standard excision would provide a poor cosmetic outcome. Further, as a surgical specialty within dermatology requiring multidisciplinary skills, it will improve significantly with the evolution of immunohistochemical staining and advances in digital technology²⁴.

Hedgehog Pathway Inhibitors

While MMS is the favored *surgical* treatment for more complex cases of basal cell carcinoma, pharmaceutical treatments known as “hedgehog pathway inhibitors” are a new method of treatment introduced in the last decade. These inhibitors are unique in that they are a targeted “anti-BCC” drug that are hoped to provide a more targeted approach to BCC treatment than current methods.

Through the use of molecular and genetic studies, it has been demonstrated that most basal cell carcinomas harbor mutations in the hedgehog (Hh) signaling pathway, thereby leading to a proliferation of basal cells²⁵. Notable about these genetic alterations is their commonly causing the loss of function of patched homologue 1 (PCTH1), which acts as an inhibitor of signaling from smoothed muscle homologue (SMO)²⁵. The role of currently approved Hh inhibitors is to suppress this aberrant signaling by binding to SMO²⁵. What’s important to note is that aberrant Hh signaling has been implicated in *several*

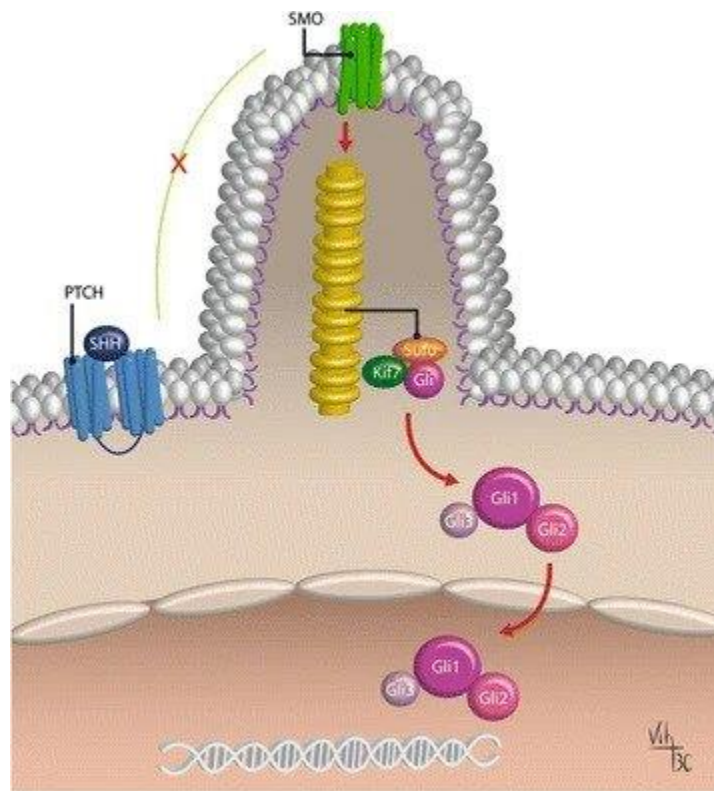
forms of cancer, not merely that of the basal cell variety²⁶, but the role of dysregulation in this pathway and oncogenesis was first noted in BCC nevus syndrome²⁷. BCC nevus syndrome is thought to be an inherited condition relating to mutations in Hh signaling, particularly those associated with PCTH1²⁷.

The Hh gene was first identified in 1980 through genetic analysis of the fruit fly *Drosophila*, where it was demonstrated to be an essential signaling pathway for organogenesis- a conserved mechanism from flies to humans²⁸. It was determined in the 1990s that Hh proteins encoded from the gene (one protein in *Drosophila*, and three in humans) were crucial in maintaining tissue polarity and population of stem cells²⁸ during embryonic development.

Based upon these characteristics Sonic Hedgehog, one of the three proteins above, is now understood to be a morphogen, a chemical vital in embryological development that determines organ development and cell specialization²⁹. In adulthood, this chemical retains importance in preserving stem cells, but is also noted for its role in several forms of cancer. The activation of the Sonic Hedgehog pathway occurs via two means, the canonical and non-canonical signaling pathways, with the former being the pathway by which current approved Hh inhibitor drugs are understood to target. The canonical pathway occurs via the binding of glycoprotein Sonic Hedgehog to PCTH1 (see **Figure 6**), leading to the deactivation of PCTH1²⁶. This deactivation leads to PCTH1 reducing its inhibitory function over SMO, resulting in the activation and

nuclear localization of glioma-associated transcription factors (the Gli labeled items in **Figure 6**), which if over-expressed can lead to oncogenesis²⁹.

Figure 6: Canonical Hh-Signaling Pathway: Activation of Hh pathway occurs via Sonic Hedgehog (SHH) binding to PTCH. Upon binding, PTCH stops inhibition of SMO, leading to signaling cascade²⁶



The first generation of Hh pathway antagonists were actually discovered as a consequence of the discovery of a potent teratogen isolated from corn lily plants (*Veratrum californicum*). Lambs that consumed this plant produced offspring with severe birth defects due to the presence of cyclopamine produced

within this vegetation²⁷. Subsequent experiments with this compound demonstrated an inhibition of tumor proliferation, and thus pharmaceutical applications were pursued. Unfortunately, the safety profile of cyclopamine was poor, with oral administration leading to severe side effects, including death, in mouse models²⁷. Further modifications of cyclopamine, however, led to synthetic derivatives- chiefly vismodegib and sonidegib²⁷. In examining the chemical structures of vismodegib and cyclopamine side by side (see **Figures 7-9**), one can see the similarity in the placement of their hydrogen bonding groups, which play essential roles in their function of binding to SMO³⁰.

In discussing the development of vismodegib and sonidegib, the two Hh pathway inhibitors that have received FDA approval for BCC treatment, it is important to make note of the fact that they are not the only compounds outside of the already mentioned cyclopamine within their classification. As of yet, over 50 compounds have been noted as playing roles as Hh pathway inhibitors, many of which have binding profiles that differ from vismodegib, sonidegib, and cyclopamine in not binding directly to SMO²⁹. It can be concluded that there may be many alternative formulations possible of Hh inhibitors which may offer even greater safety profiles and efficacy that have yet to be utilized.

Figure 7: Chemical Structure of Cyclopamine³¹

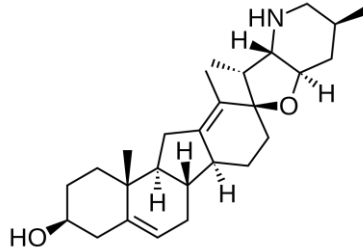


Figure 8: Chemical Structure of Vismodegib, Erivedge®³²

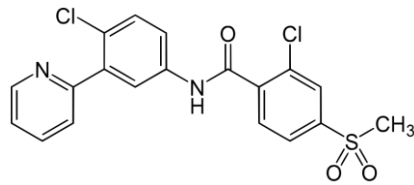
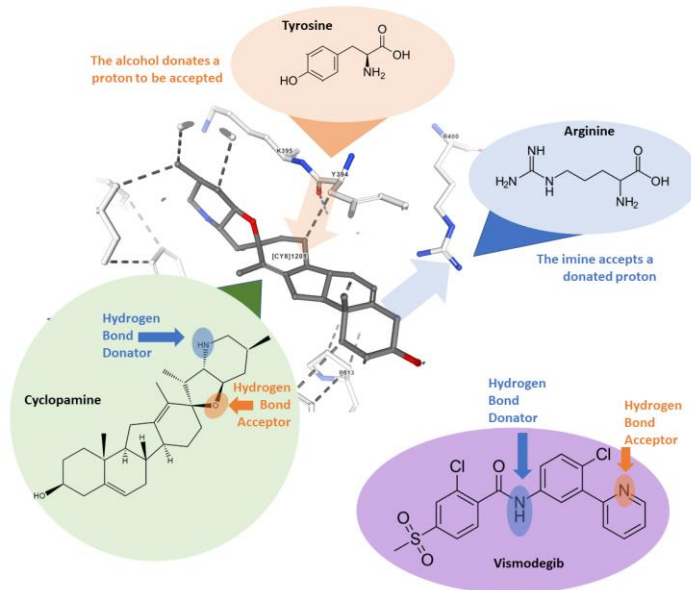


Figure 9: Similarities in Structure Between Cyclopamine and Vismodegib. Both Act Via Binding to SMO.³⁰



In 2012, vismodegib was approved by the FDA, and produced under the commercial name *Erivedge*® by Genentech, making it the first oral medication for adults with metastatic or locally advanced BCC (laBCC)³³. As has already been noted, metastasis of BCCs is exceedingly rare. One study notes that until 2019 only 350 instances of metastatic BCC have been reported in the United States, and even among these cases there is reason to speculate the number of *bona fide* diagnoses, lowering the true number of cases even further³⁴. It must be assumed then that vismodegib is primarily intended to be prescribed in instances of laBCC.

In reviewing indications and usage recommended by the manufacturer, they note that vismodegib is indicated “for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma *that has recurred following surgery* or who are not candidates for surgery and who are not candidates for radiation³⁵. In discussing the outcome of treatment, the manufacturer also notes that vismodegib is determined to have had a positive outcome of use in instances in which, after 6 months of total treatment, the BCC is determined to have *shrunk*, with an alternative outcome of the BCC having no further visible sign of occurrence³⁵ .

As far as prescribing information, the manufacturer’s recommendation is that the patient take one 150mg dose of vismodegib per day for as long as side effects are tolerable and as long as it is continuing to “work”³⁵. In one clinical study noted by the manufacturer (n = 104), half of the participants took

vismodegib for greater than 10 months, with some patients staying on the medication for as long as 19 months³⁵.

As vismodegib is a fairly recently approved medication, the indications for use in a clinical setting are still being determined. LaBCC are a fairly open classification of BCC, as will be discussed later, and the determination of this diagnosis is likely to only be made after other treatments have been attempted and failed.

In one review of indications for use of vismodegib in clinical practice, it is specified that vismodegib is explicitly recommended for laBCC in patients that have exhausted surgical and radiotherapy, which is more likely to have occurred when the lesion is greater than 2cm in diameter, has a particularly aggressive growth pattern, or is located on the head or neck³⁶. In this same review, however, there is a recommendation that further investigations be pursued in patients that may not necessarily be unable to undergo surgical treatment, or that vismodegib be prescribed in combination with radiotherapy or topical chemotherapies³⁶.

As Mohs surgery and vismodegib appear to be approaching a point of intersection in the decision-making process for the treatment of recurrent and laBCC, it is worth critically examining their efficacy and factors for consideration, as well as where future treatment protocols might be directed. Before that, however, recurrent and laBCC must be further defined.

ADVANCED CASES OF BASAL CELL CARCINOMA

Recurrent and locally advanced BCCs have a wide range of presentations due to their often being given these labels after failure to treat/excise, as opposed to subtype noted at first biopsy. There are, of course, subtypes which are notable for being more difficult to treat by simple excision, such as in the case of morpheaform BCC, noted early, and rarer forms such as basosquamous BCCs³⁷. Further, less aggressive and common subtypes which occur in areas where more conventional treatments are more difficult are more likely to experience recurrence. Additionally, a BCC does not need to have necessarily been treated previously for it to be considered locally advanced. For example, as in the case of a lesion that has been allowed to develop for many years before confirmation via biopsy⁹.

Although malignancies of the skin are among the most readily visible for both patients and non-specialist clinicians, they can readily go undiagnosed for long stretches of time. An early BCC, especially of the superficial subtype, can be mistaken for an actinic keratosis (AK), a precancerous lesion, fairly readily, or perhaps a fungal infection or similar rash¹². More insidious though is the likelihood that a patient may not think of a particular BCC lesion as problematic for months, or even years. Most especially if the BCC has long been unpainful and unobtrusive³⁸. In one particular instance, a 66 year-old patient from Poland had demonstrated a 9 year history of a slowly growing lesion in the right buccal

region, leading to severe stabbing pain, pronounced disturbances in general nutrition, and severe weight loss as the lesion had ulcerated so extensively that it was difficult for the patient to eat³⁸. Though such lengthy case histories are not common, they demonstrate how a lesion so rarely demonstrating metastasis can become so highly destructive.

The classification of a BCC as “severe” or “advanced” should be noted as generally lacking any form of standardization, as BCC cases that reach a greater level of complexity tend to differ greatly from one another⁹. As a result, one convening board of dermatologists, oncologists, plastic surgeons, and other pertinent specialists in the UK have sought to introduce a proposed clinical definition for complex BCCs⁹. This committee’s review of the BCC and how both tumor and patient factors direct treatment outcomes led to the generation of a general criteria outlined in **Table 2**. Beyond clarifying criteria for which a clinician can make a diagnosis of a complex BCC, this committee also concluded that for the sake of clarity these complex cases should be referred to as “advanced basal cell carcinoma”⁹.

Treatment options recommended for advanced BCCs come in several forms, albeit not nearly as many as might be offered for a non-advanced BCC. Luckily, though BCCs are fairly commonplace as previously identified, those that are considered “difficult to treat”, involving vital structures or particularly difficult to resection, are cited to comprise ~5% of all BCC cases, and those that are locally advanced only ~0.8%³⁷. For those cases which are within these two

categories, the case changes from one purely dermatological to one that might require the involvement of a multi-specialty team, where possible.

Disease Factors	Patient Factors
Tumor Size (e.g., giant BCC)	Patient Age (e.g., radiotherapy in young patients)
Tumor Location (e.g., Tumors of the Face, Around Eyes or Nose)	Patient Performance Status (e.g., frail patients)
Number of Tumors	Quality of Life Effects of Treatment (e.g., poor cosmetic outcome)
Tumor Subtype	Patient Opinions Regarding Treatment
Likelihood of Successful Treatment (e.g., Recurrent BCC)	Presence of Genodermatoses (e.g., Gorlin's syndrome)
	Presence of Comorbidities (e.g., organ transplant)

Table 2: Factors Guiding a Diagnosis of Advanced BCC⁹

These teams might be composed of ophthalmologists, otolaryngologists, or plastic/reconstructive surgeons depending on the nature of the BCC and what vital structures might be affected³⁷.

A treatment option as yet undiscussed at length, and still a recommended form of treatment, primarily adjuvant (i.e., combined with surgery), for advanced BCCs is radiotherapy. This class of treatment makes use of high energy radiation

to destroy cancerous tissue, typically over a series of treatments (once a day, 5 times a week, for several weeks)³⁹. Radiotherapy is a recommended treatment for what would now be considered advanced BCCs of the face of considerable size (greater than 4 cm in diameter)⁴⁰. For lesions smaller than this, historical studies have demonstrated both a higher cure rate and patient-rated cosmetic outcome in favor of surgical excision⁴⁰. Still, it is the recommended treatment for patients for whom surgery is not recommended, generally the elderly or those with unique complications³⁷. For those with genetic variants of advanced BCCs (BCC nevus syndrome, for example) or for those where radiosensitive organs (the eye or inner ear) are too close, this treatment is generally eschewed³⁷.

Figure 10: A Locally Advanced, Visibly Deeply Infiltrative BCC⁴¹



Current treatment guidelines for advanced BCCs, where neoadjuvant therapy is still considered under review, tends to make the point of demonstrating that Hh pathway inhibitors might prove an effective therapy for cases in which

surgery and/or radiotherapy is contraindicated or otherwise inappropriate⁴². As Hh pathway inhibitors have been introduced only recently and MMS has historically been the mainstay of more advanced cases of BCC, a clear example of which can be seen in **Figure 10**⁴², the compared efficacy of these two treatments across multiple criteria is a must as treatment guidelines are ongoing and there is substantial overlap in instances in which either treatment might be recommended at this time.

MMS AND Hh PATHWAY INHIBITORS COMPARED

Medical Efficacy of Treatment

The most obvious aspect to be considered in comparing MMS and Hh pathway inhibitors is the relative efficacy of each from the standpoint of desired therapeutic outcomes.

Mohs surgery, a considerably older method of treating more aggressive BCCs has a substantial store of studies of efficacy, primarily between standard excision and MMS. In one randomized-control trial conducted across hospitals in the Netherlands, participants were randomly assigned treatment via simple excision (SE) or MMS. After a period of 5 years Mohs surgery offered a considerable advantage over SE ($p = 0.015$) in reducing recurrence among BCCs that had already undergone recurrence⁴³. Reported 5-year clinical success rates generally follow this trend, with MMS treatment of recurrent BCCs demonstrating cure rates at 94.4%⁴⁴. These are, again, BCCs which have already demonstrated some propensity to be difficult to excise.

A larger retrospective study seeking to systematically review the recurrence rates for primary and recurrent BCCs across five studies (wherein a total of 2060 total lesions were included) treated with SE vs MMS exclusively on the head and neck is also of note. However, only a fraction of the total lesions contributing to this study were considered acceptable for further statistical analysis⁴⁵. For two studies in which a total of 365 lesions were enrolled, a statistically significant difference was seen in the odds ratio analyses, denoting a

lower recurrence rate for BCC lesions treated with MMS⁴⁵. However, the patients enrolled in these studies had follow-up times that ranged significantly, from a period of 16 months to 10 years⁴⁵. This, as the authors themselves note, may have led to some skew in the statistical analysis of these older studies.

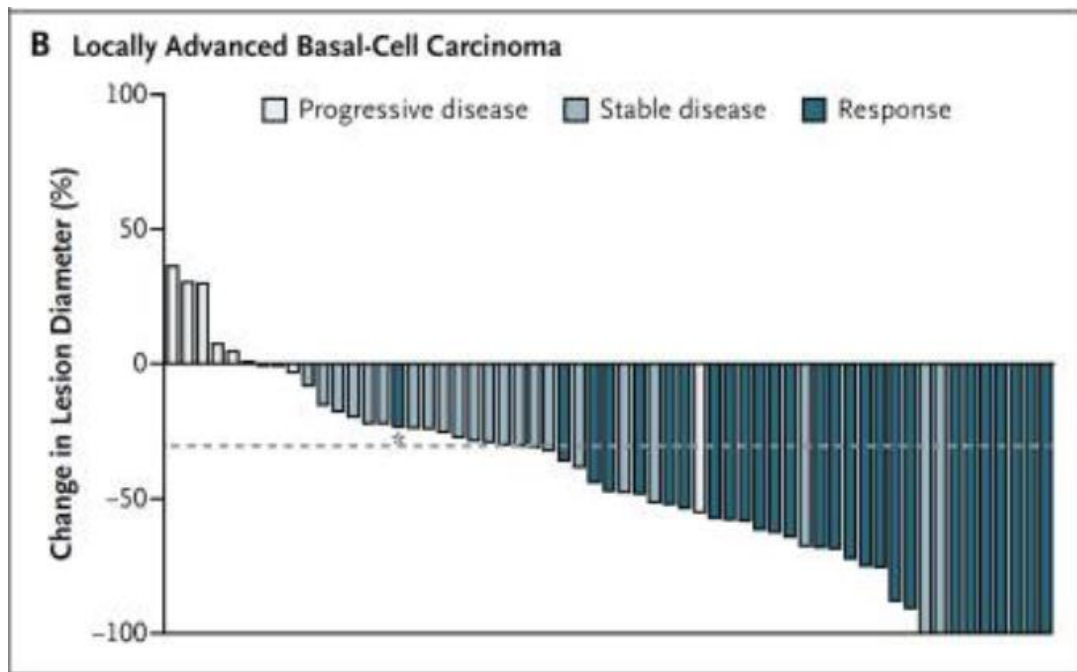
Additionally, there is surprising controversy in current literature for recommending MMS over SE for high risk (advanced) facial primary BCCs, as current evidence is considered to be of low certainty⁴⁶. With all this said, it's possible that the current use of retrospective studies to determine efficacy of surgical treatments is not sufficient, or at least offers an incomplete picture. Some authors have noted that the areas in which BCC recurrence most often occurs for both standard SE and MMS is predominantly within the "H-zone" of the face, The H-zone is the central face, eyelids, eyebrows, nose, chin, periauricular skin, and temple⁴⁷. The need to be sparing and considerate for these cosmetically important areas of the face can lead to the incomplete removal of the lesion. Further, retrospective studies may paint MMS in an unfair light, at least so far as recurrence rates are concerned, as it is most often recommended for the more advanced cases of BCC anyway^{43,47}. The conclusion offered by clinicians for these cases of recurrence after recurrence is to increase emphasis on a multidisciplinary approach. These would include a team including otolaryngologists, Mohs surgeons, neuroradiologists, pathologists, and radiation/medical oncologists with varied expertise. Such an approach has been suggested to yield a 33% probability of modification from originally intended

treatment plans⁴⁷, which suggests that the added expertise does much to steer and direct the course of treatment. Of course, this does not itself mean this modification is efficacious, merely fairly likely to occur. The same article suggests the use of novel targeted therapies (Hh pathway inhibitors) in the future, despite their having been on the market for many years prior to this article's publishing⁴⁷.

The first study undertaken to determine the efficacy of vismodegib on metastatic or locally advanced BCC, enrolled a total of 104 affected patients over a period of 13 months²⁵. These were patients for whom surgery was deemed inappropriate or inoperable by either a Mohs, otolaryngologist, or plastic surgeon²⁵. This totaled 62 percent of patients having a tumor considered *inappropriate* to surgically excise, but not *inoperable*²⁵. This means that the choice to not pursue a surgical intervention was not due to its being impossible- it was due to its being deemed less appropriate than the possible benefits to be gained from a non-surgical intervention. The results of this study determined that the objective response rate to vismodegib was 43%. The objective response rate was defined as decrease in size of 30% or more or complete resolution of ulceration. This finding was statistically significant degree of difference from the null hypothesis of 20%²⁵. **Figure 11**, produced by the aforementioned study coordinators, demonstrates the change in size for the 63 participants included in the efficacy study- where change in size was assessed by measuring externally visible dimension²⁵. The drug itself was dosed at 150 mg once daily, given by mouth, and administered over variable treatment times depending on patient

tolerance of treatment. Response to vismodegib was given defined as progressive (BCC continuing to proliferate), stable (unchanged or reduced in size at largest diameter less than 30%), or responsive (achieving a resolution of ulceration or reduction in diameter greater than 30%), with variation from these parameters dependent upon if only a partial response was achieved ²⁵.

Figure 11: A Waterfall Plot of Maximum Tumor Shrinkage for Locally Advanced BCC Post-Treatment with 150 mg daily Vismodegib, As Described in Sekulic et al. ²⁵



The median duration of response for laBCCs studied in this cohort was 7.6 months, with 54% of specimens biopsied among the laBCC cohort demonstrating no residual target lesions²⁵.

A larger subsequent study focused on lesion response to vismodegib, and safety profile of treatment demonstrated a higher response rate of 68.5%. A

complete response of 33.4%- patients enrolled in this study were permitted to continue receiving vismodegib until it was determined to be unsafe- with a median treatment time of 8.6 months (ranging from 0 to 44 months)⁴⁸. The safety profile will be discussed at length later when compared to that of MMS.

In comparing the two methodologies it's clear that MMS is significantly better. For a patient for whom a surgical excision is not completely ruled out, it is not prudent for a clinician to recommend treatment via vismodegib over MMS. In examining the manufacturer's definitions for what might be considered a locally advanced BCC, they define one as a BCC that has had *any* recurrence, in addition to a BCC that would be cosmetically disfiguring if treated surgically⁴⁹. Another consideration is the overall length of treatment. MMS is on the order of hours. The treatment time for Hh inhibitors, like vismodegib, is months.

An additional limitation in properly assessing efficacy of vismodegib in comparison to MMS is the limited timeline for which the Hh pathway inhibitor treatment has been on the market. Longitudinal studies assessing long-term instances of recurrence post-treatment are not nearly as numerous.

For patients for whom surgery and radiotherapy are not possible, or not desired, vismodegib may yet prove to be an important component of their treatment.

Adverse Effects

Tantamount to efficacy of an individual treatment are the adverse effects that might be experienced by those undergoing their prescription regimen or procedure. Potential Mohs surgery complications are the same as in any outpatient surgical procedure⁵⁰. These include scarring, postoperative pain, bleeding, hematoma, infection, and necrosis⁵⁰. Additionally, there are also other risk factors introduced in the rare instance of MMS being performed under general anesthesia- which is generally avoided²¹. Patients that are poor surgical candidates in other instances are often able to undergo MMS, as it is most often performed with local anesthetic in an outpatient, office setting²¹.

In one study concerning 23 centers in which MMS was performed, minor complications and serious adverse events were reported in 0.72% and 0.02% of all MMS cases performed, respectively²¹. Among the 20,821 cases in this study, only four required hospital admission and none involved permanent disability or death of a patient²¹. These hospitalizations were due to complications relating to infection as opposed to an emergent adverse event during procedure²¹.

Further studies comparing the incidence of complications during Mohs surgery in hospital settings vs. those in an office, demonstrated that both settings are equally safe. Thus, Mohs surgery can be safely performed away from larger multi-disciplinary treatment centers²¹. One retrospective study examining total incidence of adverse events at Washington University in St. Louis sought to determine the frequency and types of complications most often associated with

Mohs micrographic surgery. The results of this study of patients 85 and over made use of 1683 cases among 949 patients, and there were 30 complications over a 9 year period⁵¹. These complications, in order of most to least frequent, were: infection (n = 11), wound dehiscence (n = 6), hematoma (n = 6), hemorrhage (n = 5), flap necrosis (n = 1), and graft necrosis (n = 1), with a total complication rate of 1.78% per case⁵¹. Thus, Mohs surgery is a safe procedure with little in the way of severe adverse events. Even among the very elderly, the procedure is well-tolerated.

Vismodegib presents a very different safety profile than MMS. Its side effects include: blisters of the skin or mouth, sores within the mouth or on the genitals, fever or flu-like symptoms, enlarged lymph nodes, skin pain or burning, muscle spasms, hair loss, vomiting, joint pain, decreased appetite, and others⁴⁹. Like the other Hh inhibitor, cyclopamine, vismodegib may cause severe birth defects or stillbirth among females who become pregnant⁴⁹. Manufacturer guidelines specify that females who take vismodegib should use birth control for two years after their final dose, while males who undergo treatment must use contraceptives due to the presence of the drug within semen⁴⁹.

The most common side effects reported with vismodegib were muscle spasms (66%), hair loss (62%), change in taste (55%), decreased weight (41%), and decreased appetite (25%)⁴⁸. The median age of study participants was approximately 68 years old⁴⁸. One notable adverse event that was not noted to be of statistical significance was an increased risk of squamous cell carcinomas

after exposure to vismodegib⁴⁸. The study notes that after discontinuation of vismodegib the prevalence of ongoing adverse events was significantly curtailed with all of the most common side effects having incidence rates below 9%⁴⁸. Lastly, 46 patients experienced fatal events over the course of the study, with seven of these being considered related to the use of vismodegib, though each case demonstrated the presence of comorbidities/risk factors⁴⁸. This is striking when compared to Nemer et al., the counterpart study for MMS, as there were no major complications (death/loss of function) of any kind⁵¹.

A Germany study investigated the safety and effectiveness of vismodegib, in approximately the same age group (71.5 years)⁵². Of a total of 66 patients only 20 completed the study⁵². A total of 340 adverse events were noted, affecting 95.5% of patients within the study. Most of these events were mild-to-moderate, but 22 events affecting 15 patients (22.7%) were deemed serious⁵². The adverse events of this study mirrored those of Basset-Séguin et al. cited above, in order of frequency as well as approximate percentage affected⁵².

In spite of the range of adverse effects noted during the course of this study, the investigators make note of the fact that vismodegib appears to have a manageable safety profile, where no previously unknown adverse effects were determined over the course of the study⁵². The investigators' findings were apparently entirely expected, and though varied and severe when compared with MMS, are an expected consequence of treatment.

A smaller retrospective study with 11 participants found that further complication of these side effects must be considered. When patients discontinued and restarted therapy, there was a noted loss of efficacy among those with laBCC⁵³. The reasons for this loss of efficacy are not understood. This is an important consideration, as severity of adverse events was the cause of withdrawal for the majority in this study⁵³. The investigators in this study noted that the most common side effects were not controllable using other medications. Further, they are a direct consequence of the drug's mechanism of action on the Hh pathway⁵³. The implication of this finding is that Hh pathway inhibitors in general will likely cause similar side effects, and that these effects may not be exclusive to vismodegib.

One case withdrawal followed a patient with a BCC, present for 6 years, which was treated with vismodegib for fear of cosmetic deformity following surgery. After a 6-month course of daily vismodegib administration at standard dose, the patient discontinued therapy due to alopecia. However, clinical response was noted and a punch biopsy and histological evaluation demonstrated a benign histological evaluation, indicating full removal of BCC⁵⁴. 6 months thereafter, a recurrence was confirmed via biopsy and vismodegib was readministered for 6.5 months before the patient again discontinued treatment due to alopecia⁵⁴.

In comparing MMS to vismodegib therapy, it has been clearly demonstrated that MMS has a far lower probability of adverse events occurring

over the course of treatment. Furthermore, MMS is a short procedural encounter as opposed to months of continuous treatment. Severe vismodegib side effects may contribute to incomplete treatment of laBCC due to patient drug discontinuation. New Hh-inhibitors will likely exhibit a similar frequency and range of side effects, as these effects are an inherent risk of targeting this pathway.

Economics/Cost

Efficacy and side effects are often treated as the metrics of greatest importance in evaluation of medical treatments, but it is the accessibility of these treatments, both in terms of cost and general availability which will be the among the considerations to the patients themselves.

There is a fair amount of discourse in the literature concerning cost of Mohs micrographic surgery relative to simple excision. The clinical benefits must be considered against the burden of cost⁵⁵. In years past the out-of-pocket costs associated with MMS and simple excisions were about equal but this is slowly changing. Patients are now being made more financially responsible for their treatment as reimbursements to surgeons have decreased⁵⁵. As these reimbursements have decreased, the decision to utilize MMS now reflects economic need as opposed to a purely clinical advantage. Compensatory reimbursements for the treatment of high risk or recurrent nonmelanoma skin cancers are not increased over lower risk cases⁵⁵.

A more recent investigation into the economics of skin cancer broke down the average cost of treatment for various forms of skin cancer management using data from the Centers for Medicare and Medicaid Services. This study mentions that the efficacy of simple excision to Mohs surgery is equally well treated by either procedure⁵⁶. This is in contrast to the differing costs these two treatments.

Mohs surgery has an average Medicare payment of \$424 (+/- \$90) for the first stage for areas most likely to be considered high risk/advanced (H-zone,

genitalia, etc.). Subsequent stages are priced at \$306.90 (+/- \$48.87)⁵⁶. This is contrasted by normal skin excisions being priced at \$131.90 (+/- \$23.11) for 0.5 to 1.0 cm margins and \$240.50 (+/- 73.02) for excisions with margins up to 4 cm⁵⁶. The excisions also require pathology services costing \$68.37 (+/- \$11). The overall conclusion of the investigators was that MMS was 2-3 times more costly than a standard excision. There is significant variation in the US of how often MMS was the recommended course of treatment suggesting non-clinical considerations are a significant reason for treatment choice⁵⁶. The use of MMS has continued to be a hotly contested area within the field of dermatology, primarily as a consequence of its increased utilization in spite of a higher cost⁵⁷.

Vismodegib is no less a subject of controversy due to its associated cost. Upon its receipt of FDA approval, vismodegib was priced by the manufacturer at a cost of \$7500 for a one month supply of once-daily capsules³³. The duration of treatment for the use of this drug varies, but the general expectation is that a patient would pursue a 10-month course. This puts the average cost at \$75,000 for the total course of treatment³³. This was, of course, the price for 2012. The latest price estimates, offered by retail specialty pharmacies, was at \$14,893.80 for a 30 day supply⁵⁸, putting the average course of treatment at approximately \$148,938. These are staggering costs when compared to Mohs surgical procedures. However, vismodegib is a first-in-class systemic therapy, with a far more specific clinical utility at present. Pharmacists reviewing various efficacy criteria for vismodegib as early as 2013 have noted that this, in addition to

aforementioned side effects, is among the greatest considerations for use of this drug in a clinical setting⁵⁹. The lower cost of repeated surgical excision would make vismodegib an economically unattractive choice even for lesions which are highly complex and difficult to excise⁵⁹.

One particular case on a policy-level, produced by the National Centre of Pharmacoeconomics (NPCE) for Ireland, assessed consideration for reimbursement of vismodegib therapy under Ireland's medical insurance scheme. This consideration, conducted in 2013, focused primarily on medical efficacy of treatment when compared to overall cost, not considering the effects of adverse effects on the quality of life of patients surveyed in their review of cost-effectiveness of the treatment⁶⁰. The conclusion of the NPCE's review demonstrated a general skepticism with initial clinical trials of vismodegib. It noted if an estimated 51-57 patients in Ireland were to be diagnosed with an advanced BCC annually and prescribed vismodegib, it would have a budget impact peak at one point of 3.6 million euro in one year. The report did not recommend vismodegib for reimbursement⁶⁰. Four full years later, however, the national insurance scheme approved vismodegib for reimbursement following confidential price negotiations⁶⁰. Among peer insurance schemes, vismodegib received approval for reimbursement from Canadian authorities, but not the United Kingdom. The UK's conclusion demonstrated similar reservations as those seen in Ireland's report^{61,62}

The approval of vismodegib into national health scheme coverage is an important subject in considering the cost of vismodegib as these are decisions of policymakers that affect the use of a vismodegib therapy for years to come. For countries with public health schemes, if vismodegib is not recommended for approval, it is highly unlikely that it will be used in that country. Note that where vismodegib has failed to receive recommendation, Mohs surgery has been recommended^{63–65}

MMS is clearly more cost-effective than vismodegib, but it is not without controversy. MMS has attracted attention as a treatment offers a marginally more efficacious treatment at a considerably higher price point than SE. Still, its cost is dwarfed by that of vismodegib, which is likely to be among the greatest concerns to a clinician in deciding the course of treatment for a patient with an laBCC where surgical treatment is to be considered inappropriate. Perhaps if vismodegib had a lower price point it might attract greater attention for the treatment of more difficult laBCC, for example those located on the head and neck. In those cases, it might rival Mohs surgery in spite of its adverse effects.

Availability of Treatment

Availability of treatment is as worth of consideration as cost of treatment. Availability is another barrier to which therapies may not be available in spite of medical efficacy and tolerability. This availability need not be merely defined as the proximity of patients to treatment but can be more broadly defined as acknowledging barriers to access for patients.

For Mohs surgery there may be geographical barriers between specialized surgeons capable of performing MMS and patients that require it. One study from 2014 noted that there were an estimated 2,240 dermatologists performing MMS being compensated through Medicare, from which 2,118 (94.6%) were determined to be residing in metropolitan areas, 111 (5%) in non-metropolitan areas, and 11 (0.4%) in rural areas⁶⁶. Further, this study also noted that only 49.9% of surgeons who performed Mohs micrographic surgery had undergone fellowship training via the ACMS, with 27% belonging to the ASMS, and the remaining 22.9% having no affiliation⁶⁶. ACMS and ASMS are the two certifications through which a dermatologist can be determined to have proficiency in Mohs surgery. The overall conclusion of this study was that there was a clear shortage of dermatologists trained in Mohs surgery, and that those that practiced in rural areas were disproportionately without certification, indicating a lack of formal fellowship training⁶⁶.

Vismodegib, requires monitoring for adverse effects. This implies regular follow-up and therefore access to a dermatologist. It does not require a specially trained surgeon. When one precludes cost as a factor, vismodegib is highly accessible when compared to MMS, with distribution handled in such a way that the only real barrier to access is the ability to receive mail, with multiple specialty pharmacies and distributors at play⁶⁷.

The timelines for treatment for both differ substantially. A course of treatment with vismodegib, a high-risk medication, should be followed-up with regular dermatological checkups. With MMS, and out-patient surgical procedure, in spite of its requiring travel to a qualified surgeon, is perhaps only a few hours in length.

Patient Satisfaction

The final criterion, which is often among the last considered, is patient satisfaction for each method of treatment. Patient satisfaction is often a difficult metric to determine, but self-reported questionnaires are among the best means of determining patient satisfaction. For Mohs surgery, patient satisfaction is, after cure-rate, the most scrutinized metric in literature pertaining to dermatological surgical methods. Given that Mohs surgery places an increased emphasis on cosmetic results when compared to simple excisions, this is of no surprise.

One study which sought to uncover patient satisfaction based upon form of treatment for NMSC evaluated 834 total patients. It found that among ED&C, Mohs, and simple excision, treatment with Mohs surgery increased the long-term satisfaction⁶⁸. When examining the predictors of patient satisfaction with Mohs surgery, where a total of 339 patients were assessed via survey, one study determined that general satisfaction with Mohs surgery was high for 76.1% of patients (with overall satisfaction rates at 4 or higher on a 5-point scale)⁶⁹. One year after the procedure, where 232 patients responded for follow-up, general satisfaction was noted at 81%⁶⁹. Among the factors noted as being associated with a higher satisfaction score included a positive correlation with age (older patients were generally more satisfied with the outcome), and higher perception of having been involved in treatment decision-making. Surprisingly,

the greater the number of surgical stages (i.e. subsequent surgical excisions) required, the more the patient felt they were being taken care of⁶⁹.

Comparatively fewer studies have been undertaken to determine patient satisfaction and/or quality of life associated with treatment with vismodegib. One study that sought to determine quality of life (QOL) tied to treatment with vismodegib, with a study population of 56 patients, had participants and their family complete a self-administered questionnaire⁷⁰. The median duration of treatment was 6.5 months, with questionnaires distributed before treatments and after 6 months⁷⁰. Of the 56 patients, 41 were determined to be in complete remission, with 11 patients experiencing a partial remission, and four patients having discontinued treatment entirely⁷⁰. Though 45 (80.3%) of the participants experienced adverse effects, QOL was determined to have improved significantly not only for the patients themselves but also their families. The most significant area of QOL improvement was with emotional distress⁷⁰.

Overall, in spite of significant differences in occurrence of adverse effects and differing cure-rates, the overall quality of life/patient satisfaction of those that underwent either treatment have been demonstrated to be fairly high. Perhaps in the case of vismodegib this may be attributed to the fact that vismodegib might have been considered a treatment of last resort, and therefore had improved the well-being of patients where other treatments had failed previously.

DISCUSSION AND CONCLUSION

Vismodegib and Mohs micrographic surgery are substantially different methods for treating locally advanced basal cell carcinomas. In spite of their both being recommended for the treatment of primary advanced basal cell carcinomas, there are few instances in which only one or the other are attempted. The most notable among these instances, where there is choice of either vismodegib therapy or MMS for an advanced BCC, is periocular BCC⁷¹. An example of periocular BCC is shown in **Figure 12**.

Figure 12: Periocular Basal Cell Carcinoma⁷²



Periocular basal cell carcinoma is a fairly uncommon form of BCC. As the name describes, periocular BCC is defined as BCCs located proximal to the eye, and they represent about 20% of all BCCs of the head and neck region⁷¹. Due to

the fact that this area is highly sensitive, with little in the way of healthy tissue that can be excised, BCCs treated in this region are at high risk of recurrence⁷¹. Further, if these lesions go untreated there is the risk of functional and cosmetic defects, as well as a 2-4% risk of ocular invasion⁷¹. As mentioned earlier, for instances of advanced BCC around areas that are particularly sensitive, multidisciplinary teams are highly recommended. Thus, periocular BCCs require an ophthalmic consultation.

Until the introduction of vismodegib to the market, advanced forms of BCCs like this were more or less confined to treatment with Mohs surgery, perhaps combined with radiotherapy (though there are few guidelines for this)⁷¹. One study in particular that sought to examine the efficacy of vismodegib for periocular BCC, where surgery would prove too challenging or inappropriate, demonstrated that about half of the 7 study participants had their BCCs resolve over the course of treatment⁷³. The investigators for this study reached the conclusion that vismodegib offered a curative approach that was entirely novel. These were all patients that had anywhere from 1-4 recurrences following Mohs surgery. They had generally tolerated the medication well as the treatment windows were limited to an average of 11 weeks, significantly less than that most commonly indicated for lesions elsewhere⁷³. Among instances where Mohs and vismodegib can be compared for efficacy, this is one of the few in which vismodegib has demonstrated a novel utility, as a therapy to be combined in concert with Mohs surgery.

The determination that vismodegib had utility particularly for BCCs proximal to the eye led to further inquiries within this intersection of dermatology and ophthalmology. This led to clinical trials that sought to combine treatments for BCCs in this highly sensitive region⁷¹⁻⁷⁴. More recently, experimental protocols have made use of vismodegib for initial downstaging of advanced BCC for periods of 4 to 10 months. This allows for greater ease of MMS treatment on the reduced lesion⁷⁴. In one particular study overall response rates, as defined by standardized evaluation of solid tumor criteria, were demonstrated to be 71% on average- demonstrating an overall reduction in size and general appearance⁷⁵- with 36% of patients experiencing recurrence, the reappearance of a BCC lesion⁷⁴.

While the majority of neoadjuvant vismodegib therapy in the literature focuses on laBCCs around the eye, there are other instances in which vital structure involvement inspired the use of vismodegib combined with Mohs surgery. In one trial, where laBCC located within the H-zones (central face, eyelids nose, and general “mask areas” of face) were particularly large and aggressive, vismodegib therapy was initiated for three months⁷⁶. Vismodegib therapy caused two of the three lesions in the trial to disappear clinically, while the third was reduced substantially in size. Later Mohs surgical margins noted residual tumor nests that were cleared using the surgical method⁷⁶. This study demonstrates that for particularly aggressive cases of laBCC, combined therapy

can prove to be efficacious. However, the criteria for which combined therapy can be recommended in which situations have yet to be established.

In summary, evaluating vismodegib and MMS for their use strictly “on-label” has demonstrated that the instances in which vismodegib can be deemed to be more appropriate than MMS are fairly limited. It can be equally demonstrated that MMS may be overutilized in some practices. It does appear that open-label use of vismodegib holds a promising future in the treatment of specific forms of advanced BCC where surgical treatment alone is inappropriate. Studies demonstrating efficacy will likely take years to offer definitive answers. By that time, perhaps Hh pathway inhibitors will have entered into a more sophisticated generation, with their increased need conferring lower prices for treatment or at least fewer adverse effects.

LIST OF JOURNAL ABBREVIATIONS

Acta Derm Venereol	Acta Dermato-Venereologica
Am Fam Physician	American Family Physician
Am J Clin Pathol	American Journal of Clinical Pathology
American Journal of Health-System Pharmacy	American Journal of Health-System Pharmacy
An Bras Dermatol	Anais Brasileiros de Dermatologia
Arch Dermatol	Archives of Dermatology
Biomedicines	Biomedicines
Br J Cancer	British Journal of Cancer
Br J Dermatol	The British Journal of Dermatology
Cell Commun Signal	Cell Communication and Signaling : CCS
Clin Cosmet Investig Dermatol	Clinical, Cosmetic and Investigational Dermatology
Clin Exp Dermatol	Clinical and Experimental Dermatology
Clin Transl Oncol	Clinical & Translational Oncology
Cochrane Database Syst Rev	The Cochrane Database of Systematic Reviews
Curr. Treat. Options in Oncol.	Current Treatment Options in Oncology
Dermatol Surg	Dermatologic Surgery: Official Publication for American Society for Dermatologic Surgery [et Al.]
Dermatol Ther (Heidelb)	Dermatology and Therapy
Eur J Cancer	European Journal of Cancer (Oxford, England: 1990)
Future Oncol	Future Oncology (London, England)
Hematol Oncol Clin North Am	Hematology/Oncology Clinics of North America
Ir J Med Sci	Irish Journal of Medical Science
J Am Acad Dermatol	Journal of the American Academy of Dermatology
J Clin Aesthet Dermatol	The Journal of Clinical and Aesthetic Dermatology
J Invest Dermatol	Journal of Investigative Dermatology
JAMA Dermatol	JAMA dermatology (Chicago, Ill.)
JAMA Ophthalmol	JAMA ophthalmology
Lancet Oncol	The Lancet. Oncology
Med Res Rev	Medicinal research reviews
N Engl J Med	The New England journal of medicine
Oncol Rev	Oncology Reviews
Ophthal Plast Reconstr Surg	Ophthalmic plastic and reconstructive surgery
P T	Pharmacy and Therapeutics
Plast Reconstr Surg Glob Open	Plastic and Reconstructive Surgery Global Open
Postepy Dermatol Alergol	Advances in Dermatology and Allergology/Postępy

Postgrad Med
Postgrad Med J
Target Oncol
Yale J Biol Med

Dermatologii i Alergologii
Postgraduate Medicine
Postgraduate Medical Journal
Targeted Oncology
The Yale Journal of Biology and Medicine

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CURRICULUM VITAE

