



# Treating keratinocyte carcinomas with a combination of imiquimod, 5-fluorouracil, and tretinoin using store-and-forward telemedicine in the age of coronavirus disease 2019 to promote social distancing

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## INTRODUCTION

The recent coronavirus disease 19 (COVID-19) crisis has resulted in an economic downturn and the implementation of policies such as social distancing and shelter-in-place.<sup>1</sup> In light of these events, the US government has passed the Coronavirus Preparedness and Response Supplemental Appropriations Act. This act relaxed Health Insurance Portability and Accountability Act regulations and instituted new avenues of revenue for telehealth, including (1) real-time audio-video technology communication; (2) store-and-forward technology, which collects data to be later transmitted via virtual check-ins, email, or other digital applications; and (3) verbal/audio-only communication without images or prerecorded videos.<sup>2</sup> Moreover, latest polls have found that around two-thirds of patients are willing to try telehealth because of the pandemic.<sup>3</sup> These factors have allowed physicians to provide virtual care for patients who are receptive to such technology while adhering to newly instituted policies.

The various treatment options for keratinocyte carcinomas (KCs)—surgery, radiation, lasers, curettage and electrodesiccation, photodynamic therapy, intralesional chemotherapy, and cryotherapy—require in-person office visits for implementation.<sup>4</sup>

### Abbreviations used:

5-FU:	5-fluorouracil 2% solution
App:	application
BCC:	basal cell carcinoma
COVID-19:	coronavirus disease 2019
IMI:	imiquimod 5% cream
KCs:	keratinocyte carcinomas
SCC:	squamous cell carcinoma
TRET:	tretinoin 0.1% cream

Currently, effective treatment options for KCs that allow for entirely no in-person visits are unknown or limited. The combination of topical antitumor agents (imiquimod 5% cream [IMI], 5-fluorouracil 2% solution [5-FU], and tretinoin 0.1% cream [TRET]) with limited cryotherapy was found to be efficacious in the treatment of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).<sup>5</sup> With the recent institution of social distancing, we evaluated the use of store-and-forward technology with this combination (IMI/5-FU/TRET) for the treatment of KCs that required no in-office patient visits.

## CASE SERIES

After approval by the University of Miami School of Medicine's Institutional Review Board, we performed

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**Table I.** Characteristics of patients with cases of biopsy-proven KCs treated only through the store-and-forward app\*

Patient code	Age <sup>†</sup>	Gender	Lesion subtype	Lesion pathology	Lesion location	Lesion biopsy date	Lesion size (mm) <sup>‡</sup>	Treatment period <sup>¶</sup>	Cancer-free months <sup>§</sup>
1	82	M	sBCC	Superficial BCC	R forearm	4/15/19	15	53	12
1	82	M	nBCC	BCC eroded	L forearm	3/1/18	7	49	26
2	64	W	nBCC	BCC	R shoulder	10/29/15	5	110	>48
3	65	M	nBCC	BCC Eroded	R clavicle	2/20/20	10	47	3
4	50	M	nBCC	BCC	L post auricular	5/8/14	10	65	>48
5**	68	W	nBCC	BCC	Nasal tip	10/30/18	6	68	17
6**	54	M	nBCC	BCC	L upper lip	5/2/14	8	66	>48
7**	60	M	mBCC	Morpheaform BCC	R ear	1/29/18	5	62	26
8**	68	M	mBCC	Morpheaform BCC	R eyebrow	7/11/19	5	50	10
9	59	M	SCCIS	SCC in situ	R scalp	9/28/18	4	47	19
9	59	M	SCCIS	SCC in situ	R ear	10/18/18	6	48	18
10	45	W	SCCIS	SCC in situ	L forehead	10/18/19	7	52	3
11	60	M	ISCC	SCC	Scalp	2/3/15	6	78	>48
12	58	M	ISCC	SCC	R upper cheek	2/3/20	5	64	3
13	73	M	ISCC	SCC	L knee	2/11/20	13	38	3

ISCC, Invasive squamous cell carcinoma; mBCC, morpheaform basal cell carcinoma; nBCC, nodular basal cell carcinoma; sBCC, superficial cell carcinoma; SCCIS, squamous cell carcinoma in situ.

\*All patients applied 30 applications of the triple combination of IMI/5-FU/TRET. All patients had good cosmetic acceptability. No patient had a history of smoking or was immunosuppressed.

<sup>†</sup>Mean (standard deviation) age of 13 unique patients is 62 (9.7) years.

<sup>‡</sup>Median (interquartile range) lesion size is 6 (5,10) mm.

<sup>¶</sup>Treatment period is defined as the number of days needed to complete 30 applications of topical therapy from the date of the first application.

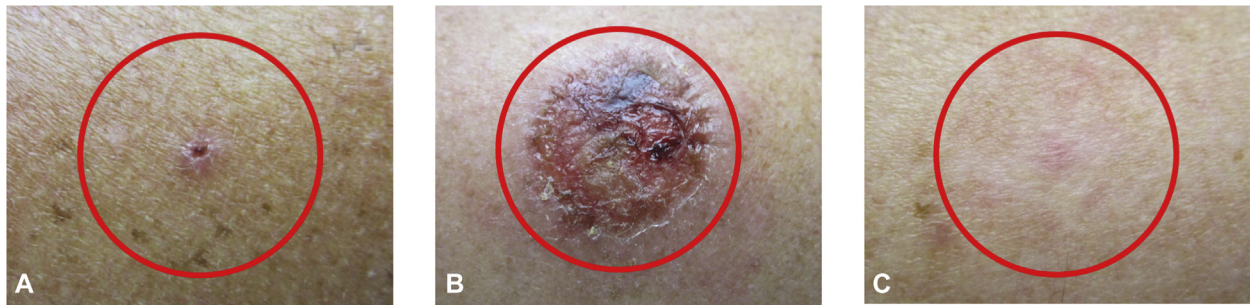
<sup>§</sup>Cancer-free months is defined as the number of months from the date of treatment completion to the date of the most recent follow-up visit.

\*\*Cases involving high-risk KCs.

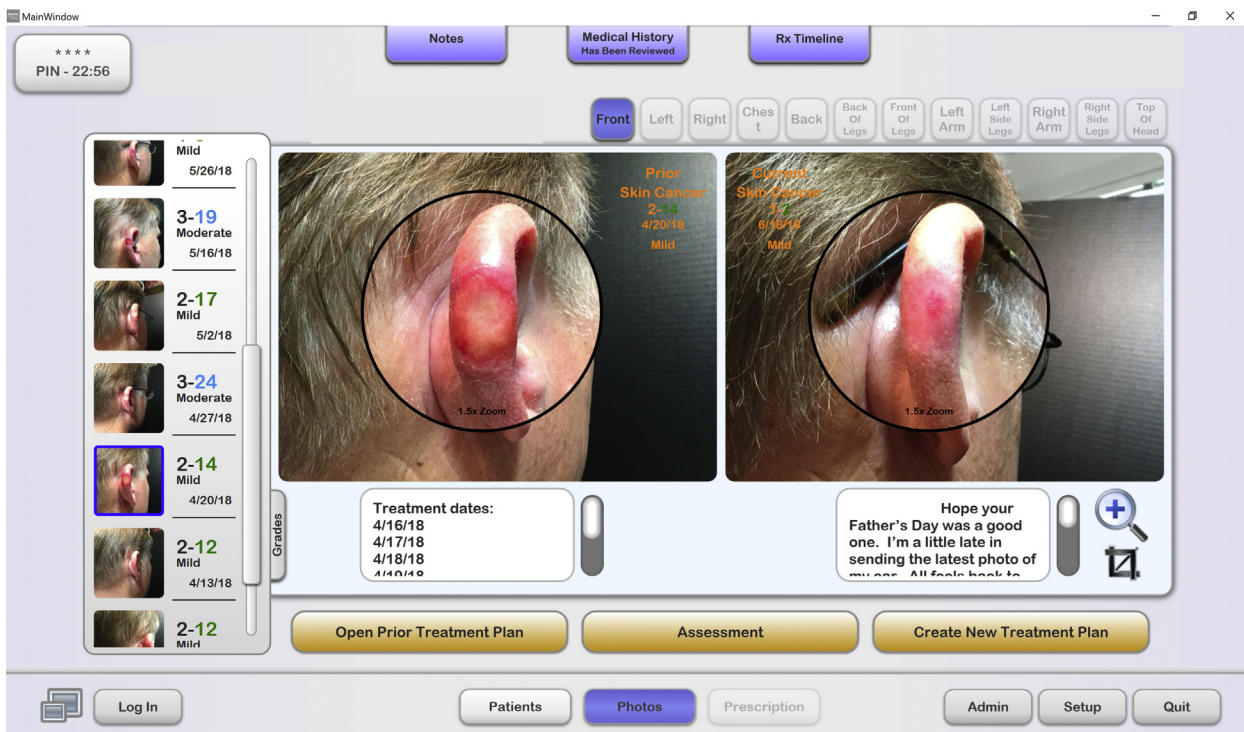
a retrospective chart review over 10 years (2009-2019). We found 701 cases of KCs that were being treated with varying combinations of IMI, 5-FU, and TRET. These cases of KCs were divided into superficial BCC, nodular BCC, morpheaform BCC, invasive SCC, and SCC in situ. All patients opted for nonsurgical treatment options, primarily for monetary reasons and an aversion to surgery, despite being counseled on surgical options and understanding the risks associated with forgoing such options. Although most cases were managed with IMI/5-FU/TRET, only 97 met the strict criteria of having IMI/5-FU/TRET treatment and at least 3 years of posttreatment follow-up to determine clearance rates. We also identified 43 cases of KCs that were treated in the last 5 years with IMI/5-FU/TRET and a store-and-forward application (app) (DermTRAC; Direct Response Medicine, LLC, Winchester, CA). Of these 43 cases, we identified 15 cases of KCs (median [interquartile range] lesion size [mm], 6 [5,10]) in 13 patients (mean [standard deviation] age, 62 [9.7] years) who had no clinic visits during their treatment period (Table I). Conversely, the other 28 cases involved patients who used the app but also had multiple in-person clinic visits during their treatment phases. For their treatment, these 13

patients (15 cases) applied one-fifth of a packet of IMI, 1 drop of 5-FU, and one-fifth of a pea-sized quantity of TRET to a bandage, which was subsequently applied to their KC overnight. The patients were instructed to use this combination for 5 days a week for 6 weeks (30 applications over 42 days) but were allowed to extend the treatment phase up to 9.5 weeks (30 applications over 76 days). Patients received training for the treatment protocol in person or through online resources (<https://www.shendermatology.com/videos>).

The 13 patients who used the app and avoided clinic visits were all able to complete the treatment protocol (30 applications) within the 9.5 weeks. Four cases involved high-risk types with clearance seen up to 10, 17, 26, and greater than 48 months (Table I). A cure was defined as the clinical lack of tumor persistence or recurrence following the completion of treatment. Four cases were identified to have greater than 4 years of cancer-free follow-up. The rest had less than 3 years, and 4 cases had limited follow-up up to 3 months. As of this time, there has been no reported recurrence of any of the tumors at these treated sites. All 15 sites were also found to have good cosmetic acceptability after treatment (Fig 1).



**Fig 1.** Images of a BCC on the posterior right shoulder treated with 30 applications of IMI/5-FU/TRET. **A**, Pretreatment shows papule of BCC (red circle). **B**, During treatment with extensive inflammation. **C**, Posttreatment shows a clearance of BCC.



**Fig 2.** Dashboard of the store-and-forward app. The patient's subjective responses in numerical severity of symptoms are recorded on the left. The comparative transformed images with magnification of a morpheaform BCC on the helix of the right ear during and after IMI/5-FU/TRET treatments are shown in the main panels.

## DISCUSSION

Despite a limited sample size, we report success for a KC treatment protocol that eliminates in-office visits and promotes social distancing. Using a nonsurgical approach and tracking patients through a store-and-forward app, 13 patients were able to have complete clearing of their KCs. The Dermtrac app was developed by engineers and validated for specific endpoints by independent dermatologists. It is implemented through a software subscription service, and interaction occurs asynchronously with the physician on a computer dashboard and the

patient on their phone app. The use of the dashboard allows the physician to remotely initiate treatment of a patient's KC with the triple combination therapy (IMI/5-FU/TRET) and monitor the patient's progress. Every 2 weeks, through the app, patients report their symptoms on a numerical scale, input topical application events, and upload treatment site pictures through template model photography (Fig 1 and 2). The app compiles all relevant data points, including subjective patient side effects, answers about inflammatory responses, application treatment logs, and comparative images from the

patient that could be transformed via scale, translation, and rotation (Fig 2). The information on the dashboard permits the physician to make decisions, authorize prescriptions, and impart standardized or custom instructions.

We chose to study the cases of KCs treated with IMI/5-FU/TRET instead of cases treated with other topical combinations. Previous studies with limited cryotherapy have demonstrated superior clearance rate of KCs with IMI/5-FU/TRET (99%) over those of IMI/TRET (94%) and 5-FU/TRET (79%).<sup>5</sup> The complete clearance rate observed in our series is commensurate with these previous studies.<sup>5</sup> Although there was marked inflammation with the topical treatments, there was full compliance with the treatment. This complete compliance level contrasts to those of other studies with monotherapy topical treatments for KCs.<sup>6</sup> Among the cohort using IMI/5-FU/TRET, lesion sizes were similar among app users and non-app users. However, mean age of patients was lower in the app user group (62 [9.7]) compared with the non-app user group (74 [10.5]), which could imply a higher comfort level with app technology with younger patients. The major drawbacks of this case series study include the retrospective model and comparatively small number of cases. Selection biases in patients involving age, cognitive ability, educational level, financial capacity, office proximity, and insurability may also be present.

With limited follow-up duration for cancer clearance, additional studies should be performed on the outcomes with telehealth and on the treatment compliance with telemedicine. Although template-model photography and transformed images allow for easy comparisons of the various stages of KC treatment, it is uncertain how effective they are in aiding the initial diagnosis of a KC without

a biopsy. Physicians considering this treatment paradigm and KC diagnosis without a visit or biopsy may direct this approach to patients with whom they have an extreme familiarity with and who have multiple KCs. This type of patient with numerous KCs may also benefit from the adaptation of telemedicine to field therapy with IMI/5-FU/TRET.

Before the outbreak, the impetus for patients to use store-and-forward apps was limited, and physicians were reluctant to use nonstandard topical therapy treatments for KCs and app technology for fear of having lower clearance rates. Our results suggest in the setting of a pandemic such as a COVID-19 outbreak, other options exist for patients who cannot be physically present with their physician.

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