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CLINICAL REPORT

Teledermoscopy in High-risk Melanoma Patients: A Comparative Study of Face-to-face and Teledermatology Visits

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Teledermoscopy is considered a reliable tool for the evaluation of pigmented skin lesions. We compared the management decision in face-to-face visits vs. teledermatology in a high-risk melanoma cohort using total-body photography, macroscopic and dermoscopic images of single lesions. Patients were assessed both face-to-face and by 4 remote teledermatologists. Lesions identified as suspicious for skin cancer by face-to-face evaluation underwent surgical excision. The teledermatologists recommended "self-monitoring", "short-term monitoring", or "excision". A 4-year monitoring was completed in a cohort of participating subjects. The general agreement, calculated by prevalence and bias-adjusted κ (PABAK), showed almost perfect agreement (PABAK 0.9–0.982). A total of 23 lesions were excised; all teledermatologists identified the 9 melanomas. The greatest discrepancy was detected in "short-term monitoring". During 4-year monitoring one melanoma was excised that had been considered benign. In conclusion, melanoma identification by experts in pigmented lesions appears to be equivalent between face-to-face and teledermatological consultation. ***Key words: melanoma; high-risk patients; total-body photography; teledermoscopy; face-to-face assessment; teledermatology.***

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Over the last 30 years, skin cancer was diagnosed more frequently than all other cancers combined (1). Melanoma constitutes less than 2% of cases of skin cancer, yet is responsible for the vast majority of deaths due to skin cancer (2). The early recognition of melanomas by periodic skin examination results in an improvement in the prognosis: thinner (< 1-mm thickness), non-ulcerated melanomas have a 5-year survival of 95%, whereas ulcerated melanomas with a Breslow thickness > 4 mm and lymph node metastasis have a 5-year survival of only 24% (3). Dermoscopy has proven to be a more accurate than naked-eye examination for detection of cutaneous melanoma (4, 5), enhancing the diagnosis of early-stage melanoma by up to 49% (5–8). Finally, a higher geographical density of dermatologists is associated with decreased melanoma mortality (9).

Consensus recommendations for the follow-up of asymptomatic patients with cutaneous melanoma were published by the American Cancer Society in 2011 (2). The expert panel recommended at least annual follow-up, with the interval shortened to 6 or 3 months in cases of new primary melanoma, multiple primary melanomas, presence of atypical naevi, and family history of melanoma (10).

A possible cost-effective alternative to face-to-face (F2F) evaluations by specialists is store-and-forward teledermatology, a method in which suspicious lesions are routinely photographed by non-specialists using cameras to acquire macroscopic and dermoscopic images, which are subsequently forwarded to teledermoscopists (TDs) for evaluation (11–15).

Teledermoscopy has proven to be a reliable method for the diagnosis of skin tumours (16–25). Di Stefani et al. (25) conducted a study of patients with multiple pigmented skin lesions (at least 3 clinically atypical naevi per patient), in which regional clinical images from each subject's back were evaluated by 2 TDs, followed by "on demand" dermoscopic images of specific lesions. The study found substantial overall agreement between F2F dermatologists and TDs in management recommendations. In another comparative study by Kroemer et al. (26), TDs evaluated clinical and dermoscopic images acquired with a mobile phone and provided management recommendations. Similarly, this study showed a high level of agreement in biopsy recommendations between teledermatology and F2F examinations. These encouraging findings have been confirmed by subsequent studies with teledermoscopy experts worldwide (27–31).

The aim of the current study was to compare the medical recommendations of a F2F at moderate-to-high risk for melanoma, compared with experienced TDs examining the same cohort of patients using total-body clinical images and dermoscopic images of selected lesions.

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PATIENTS AND METHODS

Patients were enrolled from May to October 2009 at the Pigmented Skin Lesion Clinic, Medical University of Graz, Graz, Austria. Study participants were required to meet at least one of the following factors associated with moderate-to-high risk of melanoma (32): (*i*) personal or first-degree relative history of melanoma; (*ii*) history of dysplastic naevi; (*iii*) > 5 atypical naevi; (*iv*) > 100 naevi; (*v*) lesion suspicious for melanoma. All patients provided written consent (Fig. S1[1]).

The conventional F2F total body and dermoscopic examination of all lesions, the clinical diagnosis, management, and treatment decision were performed by an individual dermatologist with expertise in the assessment of pigmented lesions. This F2F evaluation was considered to be the reference standard for all lesions that were not surgically excised. For lesions that underwent surgical excision, the reference standard was the histopathological diagnosis. In June 2013, 4 years after image acquisition, a medical chart review was performed, and all available data concerning follow-up dermatological visits, follow-up dermatological examinations, and skin biopsy or excision reports were extracted.

Following clinical examination patients underwent total-body photography, with image acquisition performed using the MoleMap® program (MoleMap Ltd, Auckland, New Zealand). Following training, the role of a "melanographer" was assumed by an experienced dermatology nurse or a dermatology resident. Without regard to the medical decision resulting from the F2F evaluation, the melanographer acquired body-sector photographs (Nikon D40 and D50 digital SLR, Nikon Corporation, Tokyo, Japan) and photographs of selected skin lesions that were: (*i*) highly suspicious; (*ii*) concerning; (*iii*) changing and/or different; (*iv*) > 3 mm; (*v*) itching, bleeding, inflamed; or (*vi*) suspicious for basal cell carcinoma (BCC) or squamous cell carcinoma.

Selected lesions underwent a close-up (Canon PowerShot G6 camera) and a dermoscopic photograph (modified Canon PowerShot G6 camera plus Epiluminescence microscopy, Canon Inc., Tokyo, Japan). Images were uploaded to a centralized server in New Zealand, which was accessible to the participating TDs. Four remote experts in dermoscopy in New Zealand, Germany and Austria (AO, MR, AB, RHW) analysed the images using a secure internet connection and an authorized computer. Histopathological examination of excised lesions was performed at the Dermatopathology Laboratory at the Medical University Graz, Graz, Austria.

The teledermoscopy experts evaluated the total body images and dermoscopic images of individual lesions and offered a medical recommendation for each lesion. The options for management of the lesions included: "self-monitoring", "short-term monitoring" and "excision".

Statistical analysis. Interobserver agreement was assessed using Cohen's κ statistics. A κ-value from 0.81 to 1.00 indicates nearly perfect agreement, 0.61–0.80 shows substantial, 0.41–0.60 moderate, 0.21–0.40 fair, 0.0–0.2 slight, and < 0 poor agreement (33).

When a very high prevalence of interobserver agreement was observed in the study and associated with a low κ value we implemented the "prevalence and bias adjusted κ" (PABAK) (34, 35) to compensate for the so-called "κ-paradox" (36). All values of Cohen's κ and the PABAK were calculated using R Statistics Software (37).

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RESULTS

Face-to-face (F2F) assessment

Seventy patients, 35 females and 35 males, age range 11–81 years (median 39 years) were enrolled in the study.

A study dermatologist evaluated each patient, resulting in the following management recommendations: 48 patients, monthly skin self-examination; 2 patients, short-term follow-up of lesions of uncertain clinical significance; and 20 patients, excision of lesions of suspected malignancy. A total of 23 lesions were excised, one patient had 2 lesions excised, and 17 patients each had one lesion excised.

Four-year follow-up

For follow-up purposes, the patients were retrospectively divided into 2 groups. The first group (35 patients) consisted of study participants with fully available 4-year follow-up information. Half of the study participants (35 out of 70), with 968 of the overall 1,922 study lesions, had a mean follow-up time of 49 months (range 47–52 months). During the longitudinal follow-up period, 4 patients in this group died from metastatic melanoma; all 4 had been diagnosed with metastatic melanoma prior to enrollment in the study.

Eight additional lesions (melanocytic naevi) were excised from 3 patients during this 4-year monitoring period. We compared the TDs' recommendations for each of these lesions. For 6 of the lesions, no recommendation for short-term follow-up or excision was documented. One lesion was recommended for short-term follow-up by TD3 and one lesion was recommended for short-term follow-up by TD1 and TD4 and for excision by TD2 and TD3.

The second group (35 patients) consisted of those subjects who did not consistently return to the clinic for follow-up examinations. Although these patients were not evaluated F2F during the 4-year follow-up period, we were able to access their medical information retrospectively. One of the study subjects, a 42-year-old woman, noticed isolated symptoms of pruritus in a pre-existing naevus, prompting a local dermatologist to perform a biopsy 15 months after she enrolled in the study. Histopathological assessment demonstrated a superficial spreading melanoma, extending to a depth < 0.5 mm without mitoses. The baseline images corresponding to this lesion had been obtained and evaluated in our study. All expert evaluators including the F2F assessment reported an unremarkable clinical appearance at the initial assessment (Fig. 1).

Image database

We performed 1,680 body sector photographs ($n = 24$ per patient) and 1,922 detail-images of single lesions,

corresponding to 70 patients. Depending on the number of selected lesions per patient (2–128 lesions, mean 27 lesions) the image acquisition procedure lasted between 30 and 90 min per patient. The participating TDs considered most images to be of excellent or good quality; 5 lesions were not evaluated due to poor image quality.

Histopathology

Histopathological analysis of excised lesions showed 9 melanomas, 12 melanocytic naevi, and 2 nodular BCC. The 9 patients (2 females, 7 males) diagnosed with melanoma had a median age of 67 years (range 35–80). The mean Breslow thickness was 1.22 mm: 3 melanomas were >1 mm thick, while the remaining lesions were less than 1 mm thick, including one melanoma *in situ*.

Twelve melanocytic naevi were excised from 9 patients (2 females, 7 males) with a median age of 37 years (range 14–41). Eleven of the 12 melanocytic naevi showed atypical architecture. The 2 nodular BCC were excised from 2 patients; a 73-year-old man and a 70-year-old woman.

Teledermoscopy

All participating TDs diagnosed the vast majority of the lesions as benign ($n = 1{,}787$) and recommended "self-monitoring". The TDs differed in the number of lesions recommended for short-term monitoring: TD1, 12 lesions; TD2, 7 lesions, TD3, 72 lesions, and TD4, 16 lesions. No single lesion was recommended for short-term monitoring by all 4 participating TDs.

A total of 51 lesions were recommended for excision; TD1, 23 lesions, TD2, 17 lesions, TD3, 34 lesions, and TD4, 28 lesions. Notably, all 4 TDs showed complete agreement in recommending surgical excision of 12 lesions, including the 9 melanomas (Fig. 2) and 1 BCC. In summary, all 23 excised lesions based on F2F evaluation were recommended for excision or follow-up by at least one TD (Table SI[1]).

Statistical analysis

The interobserver agreement between all 5 attending dermatologists (1 FTF, 4 TD) showed almost perfect agreement (PABAK 0.95).

DISCUSSION

The results of this study show overall excellent agreement of medical recommendations by expert dermatologists in the setting of total-body screening of a cohort of moderate-to-high risk melanoma patients (PABAK 0.9–0.982). Two out of 4 TDs recommended a higher number of excisions compared with F2F assessment. The duration of image acquisition ranged from 30 to 90 min per patient, representing one of the limitations of the method. The mean Breslow thickness of the excised melanomas was 1.22 mm, which indicates an advantage in the diagnosing process, because thicker melanomas can be diagnosed more easily.

One of the strengths of the study is the close interaction between the nurse and the patients, who is able to speak to the patients unhurriedly while capturing the images. An additional strength is the inclusion of a large number of lesions ($n = 1{,}922$), the participation of 4 experts in dermoscopy, the systematic study design (total-body photography, close-up photograph, dermoscopic photograph), and the inclusion of 4-year follow-up data in a subset of subjects. These strengths confirm that teledermoscopy is a reliable tool for screening and management recommendations when evaluating high-risk melanoma patients.

A good correlation between the management decisions of F2F vs. teledermatological assessment was also found in prior studies. Shapiro et al. (11) evaluated a skin biopsy triage decision of single lesions located on the face, upper trunk and affected body parts. A high agreement ($\kappa = 1$) was observed, despite the fact that only body-sector images were evaluated in each subject. Di Stefani et al. (25) used a 2-step approach to investigate the back of high-risk patients. First, clinical images

Fig. 1. Possible missed melanoma in a 42-year-old woman. Fifteen months later, the lesion was excised and reported as superficial spreading melanoma, Breslow thickness <0.5 mm. (a) Red papule in the right popliteal fossa. (b) Macroscopic image of a 5×5 mm, reddish flat plaque. (c) Dermoscopic image of lesion (b). Whitish lesion with irregular, slight brown pigmentation at the periphery of the lesion. Note the reddish colour in the macroscopic view (a, b) disappearing due to the pressure of the glass-plate of the dermoscopy camera.

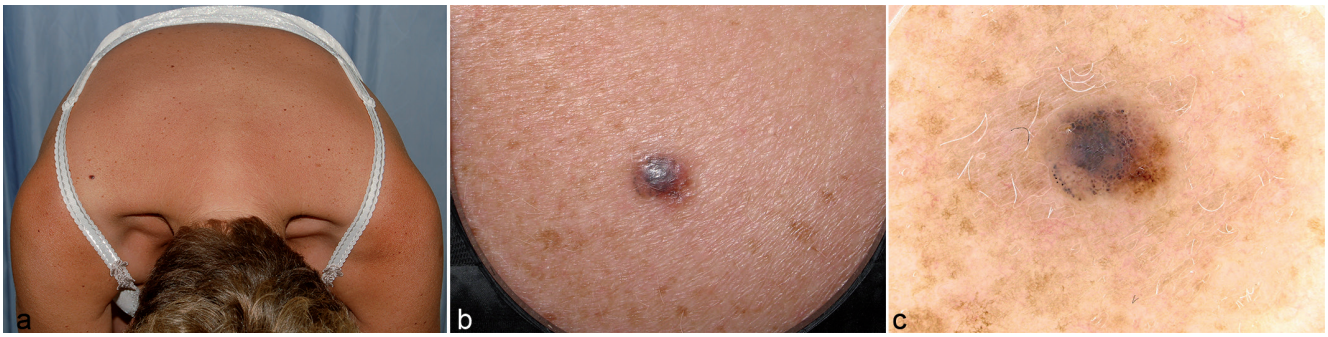

Fig. 2. Melanoma in a 50-year-old woman, which was recommended for excision by all attending dermatologists. Histopathology showed a highly suspicious melanocytic lesion, which was eventually diagnosed as melanoma (Breslow thickness 0.9 mm). (a) Brown papule on the right shoulder. (b) Macroscopic image of a 5-mm reddish brown papule with a shiny surface. (c) Dermoscopic image of lesion (b). Inhomogeneous pigmentation with a greyish patch comprising irregular dots/globules with a delicate blue-whitish veil. Note the irregular network on the right-hand side.

were evaluated by TDs, who could then request dermoscopic images of suspicious images for further evaluation. The study compared 2 inter-observer decisions: (*i*) agreement in the selection of lesions for additional dermoscopic examination, which showed a moderate concordance (κ=0.53); and (*ii*) agreement between the observers regarding management recommendations, which in general showed higher concordance (κ value 0.58–0.70).

A proven and reliable screening system in high-risk melanoma patients is the combination of total-body photography with dermoscopy. The method is called the "2-step method", was first described in 2002 by Malvehy & Puig (38) and supports the early detection of melanomas with a low rate of excisions in a population at high risk. Salerni et al. (39) described the surveillance of 618 patients at high risk for melanoma. Out of 11,396 lesions 1,152 (10.1%) were excised, 98 of which were melanomas (melanoma:benign ratio=1:10.75). In our study, a total of 53 of 1,922 lesions were recommended for excision by at least one of the 4 TDs, and an additional 9 lesions were excised during the 4-year follow-up period. Thus, a total of 62 lesions (3.2%) were excised or recommended for excision in this study, 10 of which were melanomas (melanoma:benign ratio=1:5.2). Both studies demonstrated that total-body photography combined with dermoscopy leads to the early detection of melanomas with a low rate of excisions. Similar results have recently been found in an extreme-risk population (personal history of melanoma and/or dysplastic naevus syndrome and/or confirmed CDKN2A- or CDK4-mutation) (40, 41, 44).

In 2 parallel studies Warshaw et al. (42) compared clinic dermatology and teledermatology in diagnostic accuracy and management plan for pigmented and non-pigmented neoplasms (43). Study patients included those referred to dermatology by non-dermatologists, as well as patients undergoing biopsy of a suspicious lesion because of patient request or physician recommendation. Before excision, the lesions were imaged macro- and dermoscopically. All lesions evaluated in these studies were excised and confirmed histopathologically. The diagnostic accuracy of teledermatology was inferior to F2F evaluation (67% vs. 80%), but teledermatology was equivalent or superior to F2F evaluation in management decision (70% vs. 65%). In our study the interobserver agreement on management decision between all 5 attending dermatologists (1 FTF, 4 TD) showed almost perfect agreement (PABAK 0.95).

The decision options for TDs in our study were "self-monitoring", "short-term follow-up" or "excision". In comparison with the study of Warshaw these 3 options are simplified; possibly explaining the higher concordance rate reached in our study. Another reason for this observation may be the inclusion of all benign lesions in the statistical calculations.

In our study the highest agreement between F2F dermatologists and TDs was found in the recommendations given for malignant tumours. All melanomas were recommended for excision by all attending dermatologists. One of 2 BCCs was recommended for excision by all, and the second BCC was recommended for excision by 2 out of 4 TDs.

The lowest level of agreement between F2F dermatologists and TDs was found in the management recommendation for "short-term follow-up". The low level of agreement concerning the recommendation for "short-term follow-up" may reflect variations in international practice; alternatively, the wide range could simply reflect the degree of risk comfort of the individual doctors. One might assume that a similar degree of risk comfort plays a role in the daily clinical assessment of melanocytic skin lesions by expert dermatologists. In our study, none of the lesions recommended for short-term monitoring were given this recommendation by all 4 TDs; standardization of criteria for follow-up might mitigate this variability. Notably, however, all 4 TDs diagnosed the 9 melanomas identified by the F2F assessment.

The long-term follow-up component of the study provided important information about the proposed screening model. Nine lesions were excised during this period;

8 dysplastic naevi and one amelanotic melanoma. The melanoma detected during the follow-up period was most probably missed by all 5 dermatologists, assuming that the lesion in question (see Fig. 1) was already an amelanotic melanoma at the time of initial presentation. The reason given for the excision, 15 months after our F2F examination, was new onset of pruritus; change in size or colour was not observed by the patient or her local dermatologist. The failure to recognize this melanoma F2F and by teledermoscopy is a reminder that the diagnosis of amelanotic melanoma can be challenging, particularly in the setting of MC1R phenotypes (44).

In conclusion, this study shows that teledermatological screening based on total-body photography and teledermoscopy is a useful and reliable method to detect melanomas and non-melanoma skin cancers in patients at increased risk of melanoma. This method could be a reasonable alternative or adjunct to the classical F2F examination. Teledermoscopy also provides an opportunity to improve access to experts in the field of dermoscopy for high-risk melanoma patients.

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Conflicts of interest: CC-L is a shareholder of DermSpectra, Inc. AO is a consultant and investigator of MoleMap, Nz, and provides scientific support and teledermatological reports. MR is a consultant of MoleMap, Nz and provides and teledermatological reports. HPS was supported in part by an NHMRC Practitioner Fellowship (APP1020145). HPS is a shareholder of E-derm Consult GmbH and MoleMap by Dermatologists Ltd and provides teledermatological reports regularly for both companies. The other authors declare no conflicts of interest.

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