Effect of Reflectance Confocal Microscopy for Suspect Lesions on Diagnostic Accuracy in Melanoma
A Randomized Clinical Trial

Giovanni Pellacani, MD; Francesca Farnetani, MD; Silvana Ciardo, BS; Johanna Chester, BA, BSC; Shaniko Kaleci, PhD; Laura Mazzoni, PhD; Sara Bassoli, MD; Alice Casari, MD; Riccardo Pampena, MD; Marica Mirra, MD; Michela Lai, MD; Serena Magi, PhD; Victor D. Mandel, MD; Sergio Di Matteo, MSc; Giorgio Lorenzo Colombo, MSc; Ignazio Stanganelli, MD; Caterina Longo, MD

IMPORTANCE Previous systematic reviews and meta-analyses have concluded that given data paucity, a comparison of reflectance confocal microscopy (RCM) with dermoscopy is complex. They recommend comparative prospective studies in a real-world setting of suspect lesions.

OBJECTIVE To test the hypothesis that RCM reduces unnecessary lesion excision by more than 30% and identifies all melanoma lesions thicker than 0.5 mm at baseline.

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical trial included 3165 patients enrolled from 3 dermatology referral centers in Italy between January 2017 and December 2019, with a mean (SD) follow-up of 9.6 (6.9) months (range, 1.9-37.0 months). The consecutive sample of 3165 suspect lesions determined through dermoscopy were eligible for inclusion (10 patients refused). Diagnostic analysis included 3078 patients (48 lost, 39 refused excision). Data were analyzed between April and September 2021.

INTERVENTIONS Patients were randomly assigned 1:1 to standard therapeutic care (clinical and dermoscopy evaluation) with or without adjunctive RCM. Information available guided prospective clinical decision-making (excision or follow-up).

MAIN OUTCOMES AND MEASURES Hypotheses were defined prior to study initiation. All lesions excised (baseline and follow-up) were registered, including histopathological diagnoses/no change at dermoscopy follow-up (with or without adjunctive RCM). Number needed to excise (total number of excised lesions/number of melanomas) and Breslow thickness of delayed diagnosed melanomas were calculated based on real-life, prospective, clinical decision-making.

RESULTS Among the 3165 participants, 1608 (50.8%) were male, and mean (SD) age was 49.3 (14.9) years. When compared with standard therapeutic care only, adjunctive RCM was associated with a higher positive predictive value (18.9 vs 33.3), lower benign to malignant ratio (3.7:1.0 vs 1.8:1.0), and a number needed to excise reduction of 43.4% (5.3 vs 3.0). All lesions (n = 15) with delayed diagnosed melanomas were thinner than 0.5 mm.

CONCLUSIONS AND RELEVANCE This randomized clinical trial shows that adjunctive use of RCM for suspect lesions reduces unnecessary excisions and assures the removal of aggressive melanomas at baseline in a real-life, clinical decision-making application for referral centers with RCM.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04789421

JAMA Dermatol. 2022;158(7):754-761. doi:10.1001/jamadermatol.2022.1570
Published online June 1, 2022.
Diagnostic efforts for melanoma detection focus on early and precise diagnoses, recognized as the greatest prognosis and most economic solution for melanoma.\(^1\) Dermoscopy is more accurate than the naked eye\(^2\) but is limited by numerous unnecessary excisions.\(^3,4\) The rate of benign lesions excised for every melanoma detected range from 5 to 30 lesions, depending on specialization.\(^5,6\) Specificity is improved with dermoscopy digital follow-up (DDF), with rates of melanoma diagnosis of 7% during monitoring.\(^7,8\)

Reflectance confocal microscopy (RCM) enables in vivo cutaneous examination,\(^9\) high diagnostic accuracy,\(^10-12\) and specificity improvements for equivocal lesions (30%-70%).\(^13\) Additionally, RCM appears more accurate than use of dermoscopy alone (specificity, 82% vs 42%)\(^14\) and improves the accuracy of benign recognition for equivocal lesions.\(^15\)

Skin cancer management exerts a sizable burden on health systems.\(^16\) The systematic application of RCM in the triage of high-risk patients should improve diagnostic accuracy and reduce unnecessary excisions for histopathological diagnostic confirmation, thereby reducing costs, surgical waiting lists, and delayed diagnoses. However, the clinical application of RCM has mainly been limited to retrospective and prospective observational studies producing hypothetical estimates of clinical applicability without intention to affect clinical and therapeutic patient pathways.\(^9,11,13,17-20\)

Defined prior to study initiation, this trial hypothesized that adjunctive use of RCM reduces unnecessary excisions by 30% and, among lesions assigned to DDF, melanoma is identified in less than 2% with a Breslow thickness of 0.5 mm or thinner. This study aims to assess adjunctive RCM imaging among randomly assigned equivocal lesions suspected of melanoma to either standard therapeutic care alone or with the integration of RCM, with or without DDF and RCM monitoring. Assessment includes rates of detection, in terms of the number needed to excise (NNE), rates of accuracy, delayed diagnosis, and melanoma Breslow thickness of lesions excised during DDF, based on prospective, clinical decision-making.

**Methods**

**Study Design**

This prospective, multicenter, 2-arm, randomized interventional study was conducted at 3 Italian centers: the Department of Dermatology of the University of Modena and Reggio Emilia, the Skin Cancer Unit of IRCCS Reggio Emilia, and the Skin Cancer Unit of IRCCS IRST Romagna. The study was approved by the Italian Ministry of Health and the Modena Ethics Committee, and a short, translated version of the study protocol is available in Supplement 1. This study also followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Patients’ access and clinical therapeutical pathways were similar at each collaborating center, per national and regional health care regulations. Briefly, the usual patient pathway includes access to participating dermatological units by referral from other specialists or family physicians. Standard therapeutic care includes clinical and/or dermoscopic assessment by dermatologists. In the case of equivocal lesions, defined as clinically and/or dermoscopically suspected of melanoma owing to the absence of unequivocal clinical and/or dermoscopic aspects of malignancy impeding differential diagnosis of melanoma, patients are invited to adjunctive RCM imaging for prospective decision-making; the patient is accompanied by the visiting dermatologist to a separate, dedicated consultation with an RCM technician who performs lesion assessment. Images of the skin morphology are assessed on the digital screen in real time by the dermatologist. Based on RCM features observed, the dermatologist decides whether the lesion should be sent for immediate excision or referred to DDF.

For the current study, the patient pathway was modified between August 2017 and June 2019, and consecutive patients with equivocal lesions detected during standard therapeutic care, who provided written informed consent, were then randomly assigned to either access RCM (adjunctive RCM) or not (standard therapeutic care only) at a ratio of 1:1. Unequivocal lesions (benign or malignant), hyperkeratotic or fully ulcerated lesions, and/or lesions located on mucosa or palmar/plantar areas or in skin folds not permitting the use of RCM were not included. According to patient randomization, the physician’s management decision (surgical excision or DDF) was based on standard therapeutic care and RCM or standard therapeutic care only. Lesions deferred to DDF were assessed according to standard therapeutic care with or without adjunctive RCM use at the discretion of the physician, independent of initial randomization.

Following randomization, patients who refused excision were included in economic analyses (intention to treat) but could not be included in diagnostic analyses. Patients lost to follow-up were not included in any analyses (Figure).

**Data Collection**

All collaborating centers were equipped with a handheld dermatoscope (DL4 [DermLite]), digital dermatoscope (Visiomed [Canfield Scientific]), and reflectance confocal imaging system (VivaScope 1500 [MAVIG GmbH]). Acquisision procedures have been extensively described elsewhere.\(^21\) Briefly, series of 3 or more mosaic images, including 80% or more of the lesion at depths between 10 and 40 μm below the skin surface (intraepidermal, dermal-epidermal junction, and upper dermis), were obtained. Complete scanning of each lesion took approximately 7 minutes. In case of larger lesions
Figure. CONSORT Flow Diagram

- 3175 Assessed for eligibility
- 3165 Randomized
- 1583 Randomized to standard therapeutic care plus reflectance confocal microscopy
- 1582 Randomized to standard therapeutic care
- 48 Lost to follow-up (patient did not return)
- 16 Discontinued intervention (patient refused excision)
- 0 Lost to follow-up
- 23 Discontinued intervention (patient refused excision)
- 1519 Diagnostic analysis
  - 64 Excluded from analysis
  - 48 Lost to follow-up
  - 16 Refused excision
- 1519 Diagnostic analysis
  - 23 Excluded from analysis (refused excision)

Center following study closure. Lesions were grouped as malignant (melanocytic or nonmelanocytic) or benign (melanocytic, nonmelanocytic, or inflammatory). We considered a lesion malignant if histopathological analysis returned a diagnosis of melanoma/melanoma in situ (MIS) (melanocytic) or basal cell carcinoma/squamous cell carcinoma (nonmelanocytic). We considered a lesion benign for diagnoses of nevus (melanocytic), solar lentigo, seborrheic keratosis, lichen planus–like keratosis, lichen simplex (nonmelanocytic), or other (inflammatory).

**Statistical Analysis**

**Sample Size**

We hypothesized a 7.3% proportion of melanoma identified in standard therapeutic care requiring 285 patients per arm to give 80% power (1-sided type I error of 5%). We also hypothesized a 14% proportion of melanoma identified with adjunctive RCM based on approximately 22.4% of suspect lesions in highly experienced centers being treated, requiring 420 patients per arm to give 80% power (2-sided type I error of 2.5%). Overall recruitment estimates of 3090 patients or more were calculated. No interim analyses were planned.

**Randomization**

A 1:1 randomization at enrollment was applied (computer-generated list of random numbers) by an independent statistician who was not involved in data collection; study experimenters were not involved in list generation or allocation. Randomization sequence was generated using block allocation with variable sizes (2-4) stratified by center using Stata statistical software, version 12.0 (StataCorp), with “ralloc” command.

Following written patient consent, clinicians referred to the randomization list for registration and randomization sequence. Once patient assignment was confirmed, the patient, clinician, and data analysts were aware of study allocation. The study data set was completed by each participant center, and data quality was independently reviewed by a statistician (S.K.).

**Statistical Methods**

In all calculations, melanoma included both MIS and invasive melanoma. Differences in diagnostic frequencies between groups were calculated and compared using the \( \chi^2 \) test. The NNE was calculated by dividing the total number of excised lesions by the number of melanomas. Accuracy assessment included positive predictive values (PPVs), benign to malignant and benign melanocytic to melanoma ratios, and correlations with physicians’ RCM experience (malignant lesions/lesions excised). Tests of proportions and equality of proportions for large-sample statistics were used to compare differences in NNE, based on hypothesized population value for no difference in proportions.

Analyses were performed according to the intention-to-treat principle. Subgroup analyses were summarized using descriptive statistics. Continuous variables were expressed as mean (SD) and compared using unpaired \( t \) test. Categorical variables were expressed as frequencies and compared using...
Table 1. Clinical Features for Patients With Equivocal Lesions by Randomization Group

| Characteristic                  | Total   | Standard therapeutic care + RCM | Standard therapeutic care only |
|--------------------------------|---------|---------------------------------|-------------------------------|
| No. of patients                | 3165    | 1583                            | 1582                          |
| Age, mean (SD) [range], y      | 49.3 (14.9) [18-96] | 49.0 (14.9) [18-93] | 49.6 (15.1) [18-96] |
| Gender                         |         |                                 |                               |
| Female                         | 1557    | 814                             | 743                           |
| Male                           | 1608    | 769                             | 839                           |
| Lesion site                    |         |                                 |                               |
| Head/neck                      | 148     | 63                              | 76                            |
| Trunk                          | 2167    | 1071                           | 1096                          |
| Upper limbs                    | 332     | 177                            | 155                           |
| Lower limbs                    | 527     | 272                            | 255                           |
| History of melanoma            |         |                                 |                               |
| Personal                       | 678     | 321                            | 357                           |
| Familial                       | 448     | 222                            | 226                           |
| Other cutaneous tumor          |         |                                 |                               |
| Personal                       | 343     | 158                            | 185                           |
| Familial                       | 127     | 60                             | 67                            |
| Phototype*                     |         |                                 |                               |
| 1                              | 243     | 112                            | 131                           |
| 2                              | 1597    | 820                            | 777                           |
| 3                              | 1244    | 618                            | 626                           |
| 4                              | 78      | 31                             | 47                            |
| Overall No. of nevi            |         |                                 |                               |
| <50                            | 1436    | 738                            | 698                           |
| 50-100                         | 1041    | 493                            | 548                           |
| >100                           | 688     | 352                            | 336                           |
| Overall No. of atypical nevi   |         |                                 |                               |
| <3                             | 2285    | 1143                           | 1142                          |
| 4-6                            | 467     | 217                            | 250                           |
| >6                             | 413     | 223                            | 190                           |
| Photodamage around suspected lesion | 1423 | 688                           | 735                           |

Abbreviation: RCM, reflectance confocal microscopy.

* Data missing for 3 patients.

Pearson χ² test. Pearson correlation coefficient was used to assess associations between physicians’ years of RCM experience prior to study initiation and correct identification of malignant lesions at baseline with adjunctive RCM use. A P < .05 was considered statistically significant, and r > 80% was considered a very high correlation. Statistical analysis was performed using Stata statistical software, version 14 (StataCorp).

Results

Patient Enrollment and Assignment

Between January 2017 and December 2019, a total of 3165 patients were randomly assigned to either standard therapeutic care with adjunctive RCM imaging or standard therapeutic care only. Ten patients did not give consent to randomization, directly requesting adjunctive RCM evaluation, and were not included in this analysis (Figure). For enrolled patients without immediate lesion excision, the mean (SD) follow-up was 9.6 (6.9) months (range, 1.9-37.0 months).

Patient enrollment was similar according to collaborating centers: IRCCS Reggio Emilia (n = 1140 [35.1%]), University of Modena and Reggio Emilia (n = 1105 [34.0%]), and IRCCS IRST Romagna (n = 1002 [30.9%]). Dermatologists involved in RCM image interpretation and rendering diagnoses at University of Modena and Reggio Emilia (F.F., S.B., A.C.), IRCCS Reggio Emilia (C.L., R.P., M.L.), and IRCCS IRST Romagna (V.M. and I.S.) actively enrolled patients over the entire study period. The RCM experience among the physicians ranged from 4 to 15 years prior to study initiation. Analysis of patient and lesion characteristics according to collaborating centers did not reveal any statistically significant differences.

Among the 3165 total patients, the mean (SD) age was 49.3 (14.9) years, and a personal history of melanoma was registered for 678 (21.4%) patients. Most lesions were identified on the trunk (n = 2167 [68.5%]), and less than half of all lesions had photodamage immediately around the suspected lesion (n = 1423 [44.9%]) (Table 1).

Characteristics of patients assigned to adjunctive RCM evaluation are summarized in Table 1. Just fewer than half (n = 720 [45.5%]) were sent for immediate excision. According
to the time of the DDF visit, among those sent for short-term follow-up, 101 of 564 (17.9%) were assigned excision compared with 21 of 289 (7.2%) sent for long-term follow-up. Melanoma was confirmed in 278 of 836 (33.2%) excised lesions assessed with adjunctive RCM; 144 of the 278 (51.8%) were classified as MIS (Table 2).

Among the 1582 patients assigned to standard therapeutic care only, all lesions with the exception of those in 3 patients who refused surgery were assigned excision (n = 1579 [99.8%]). Of these lesions, 294 (18.6%) were diagnosed through histopathology as melanoma, and then 178 (60.5%) of these were classified as MIS (Table 2).

### Lesions Excised, Excision Ratios, and NNE

Of all 3165 excised lesions, melanoma was identified in 572 (23.9%). The overall study NNE was 4.2. The overall PPV of an excised lesion being melanoma was 23.9% (Table 3).

Physicians’ years of RCM experience correlated very highly with diagnostic accuracy (r = 0.99; 95% CI, 0.82-0.99; P = .004).

When compared with standard therapeutic care only, the adjunctive use of RCM revealed a slightly inferior rate of melanoma detection (294 vs 278), an almost 2-fold higher PPV (18.9 vs 33.3), and an almost halved benign to malignant ratio (3.7:1.0 vs 1.8:1.0). The NNE was reduced by 43.2% with adjunctive use of RCM (5.3 vs 3.0) (Table 3).

### Diagnostic Safety

Overall, 15 of 853 (1.8%) lesions referred for DDF were revealed as melanoma. Of these, 8 (53.3%) were diagnosed as MIS, and no melanomas identified at DDF were thicker than 0.5 mm. Furthermore, the mean thickness of melanomas identified at follow-up was inferior to baseline values. Over the mean follow-up of 9.6 months, of the 3165 total lesions referred for follow-up, 101 of 564 (17.9%) were assigned excision compared with 21 of 289 (7.2%) sent for long-term follow-up.

| Characteristic                                      | No. (%)                  | Standard therapeutic care + RCM | Standard therapeutic care only | P value |
|-----------------------------------------------------|--------------------------|-------------------------------|-------------------------------|---------|
|                                                     | Total                     | 1583                          | 1582                          | NA      |
| History diagnoses                                   |                          |                               |                               |         |
| Melanoma                                            | 557 (17.6)               | 263 (16.6)                    | 294 (18.6)                    | NA      |
| Malignant, nonmelanocyticc                         | 52 (1.6)                 | 15 (0.9)                      | 37 (2.3)                      | NA      |
| Benign, melanocyticb                               | 1548 (48.9)              | 414 (26.2)                    | 1134 (71.7)                   | <.001   |
| Benign, nonmelanocyticc                            | 56 (1.8)                 | 14 (0.9)                      | 42 (2.7)                      | NA      |
| Benign, inflammatoryd                              | 63 (2.0)                 | 14 (0.9)                      | 49 (3.1)                      | NA      |
| Sent to digital follow-up                          | 856 (27.0)               | 853 (53.9)                    | 3 (0.2)                       | NA      |
| No diagnosis (patient excision refusal)             | 33 (1.0)                 | 10 (0.6)                      | 23 (1.5)                      | NA      |
| Baseline melanoma features                         | 557 (100)                | 263 (47.2)                    | 294 (52.8)                    | NA      |
| Melanoma Breslow thickness, mean (SD) [range], mm   |                          |                               |                               |         |
| 0.0                                                 | 0.17 (0.23) [0-0.8]       | 0.19 (0.24) [0-0.8]           | 0.15 (0.22) [0-0.8]           | .02     |
| 0.0-0.5                                             | 314 (56.4)               | 136 (51.7)                    | 178 (60.5)                    |         |
| >0.5                                                | 187 (33.6)               | 93 (35.4)                     | 94 (32.0)                     | .05     |
| Follow-up lesion diagnoses                         | 856 (100)                | 853 (99.6)                    | 3 (0.4)                       | NA      |
| History diagnoses                                   | 116 (13.6)               | 116 (13.6)                    | 0                             | NA      |
| Melanoma                                            | 15 (1.8)                 | 15 (1.8)                      | 0                             | NA      |
| Malignant, nonmelanocyticc                         | 1 (0.1)                  | 1 (0.1)                       | 0                             | NA      |
| Benign, melanocyticb                               | 95 (11.1)                | 95 (11.1)                     | 0                             | NA      |
| Benign, nonmelanocyticc                            | 3 (0.4)                  | 3 (0.4)                       | 0                             | NA      |
| Benign, inflammatoryd                              | 2 (0.2)                  | 2 (0.2)                       | 0                             | NA      |
| No morphological changes at digital follow-up       | 686 (80.1)               | 683 (80.1)                    | 3 (100)                       | NA      |
| No diagnosis (patient excision refusal)             | 54 (6.3)                 | 54 (6.3)                      | 0                             | NA      |
| Lost to follow-up                                   | 48 (5.6)                 | 48 (5.6)                      | 0                             | NA      |
| Follow-up melanoma features                        | 15 (100)                 | 15 (100)                      | 0                             | NA      |
| Melanoma Breslow thickness, mean (SD) [range], mm   |                          |                               |                               |         |
| 0.0                                                 | 0.16 (0.19) [0-0.5]       | 0.16 (0.19) [0-0.5]           | NA                            | NA      |
| 0.0-0.5                                             | 8 (53.3)                 | 8 (53.3)                      | 0                             | NA      |
| >0.5                                                | 7 (46.7)                 | 7 (46.7)                      | 0                             | NA      |
| Follow-up, mean (SD) [range], mo                    | 9.6 (6.9) [1.9-37.0]      | 9.6 (6.9) [1.9-37.0]          | 8 (3.4) [6.0-12.0]            | NA      |

Abbreviations: NA, not applicable; RCM, reflectance confocal microscopy.

c Basal cell carcinoma, squamous cell carcinoma, Bowen disease, and keratoacanthoma.

d Solar lentigo, seborrheic keratosis, lichen planus-like keratosis, and lichen simplex.

e Others.
patients, 39 (1.2%) refused to excise and 48 (1.5%) were lost to follow-up (Table 2).

### Discussion

This randomized interventional trial assessed the applicability of adjunctive RCM for equivocal lesions suspected of melanoma in a clinical setting and proves that unnecessary excisions can be reduced by almost half, with greater accuracy of in vivo identification of benign lesions. Furthermore, delayed diagnosis included thin melanomas only.

Data from this study are essential for the ongoing discussion regarding the applicability of advanced technologies in routine melanoma detection among equivocal lesions. Our group previously assessed the integration of RCM into a diagnostic-therapeutic workflow (with centralized and immediate assessment of suspect lesions) and specific education over a 10-year period in a single province, reporting improved precision in diagnosis of approximately 100%. Meta-analyses have reported estimates of improved specificity of RCM compared with dermoscopy. In 2020, Pezzini et al concluded that independent of study design, RCM has a high diagnostic power for melanoma detection (pooled sensitivity of 92%) and reduces unnecessary excisions (pooled specificity of 70%). Recent estimates propose 7.5 benign pigmented lesions are removed for each histologically confirmed melanoma. Petty et al studied the NNE for dermoscopy according to clinical setting and found that the NNE was 4-fold lower (5.85) for specialists compared with primary physicians (22.62). In the current study, all diagnoses were performed by specialists and NNE for dermoscopy was 5.3, comparing well with data provided by Petty et al. In a long-term study, Guitera et al recently reported a rate of 2.4 benign melanocytic lesions biopsied per melanoma for high-risk patients included in a strict DDF. The correlation of detection accuracy with physicians’ RCM experience suggests that, as with dermoscopy, prospective management decision-making is dependent on RCM experience. Prior to this study, most estimates of NNE calculations were based on retrospective analyses. As suggested by Privalle et al, retrospective studies based on NNE do not fully assess diagnostic accuracy because they give no insight into the number of malignant lesions that go undiagnosed and they do not consider patient preference for biopsy. This prospective, randomized study reports a slightly higher number of melanomas identified with standard therapeutic care. This minimal imbalance in diagnostic accuracy may be explained by false-positive histopathological results being more likely among higher volumes of excised lesions, potential thin melanomas undiagnosed among patients lost to follow-up, or false-negative results with RCM assessment. This study also reports prospective rates of deferred melanoma diagnoses, refusal to excise, and loss to follow-up, which are useful for procedure risk assessment.

In this study, RCM assisted in the identification of melanomas with similar mean Breslow thickness compared with standard therapeutic care while requiring just more than half of the number of excisions. Several meta-analyses have proven the advantage of dermoscopy and RCM in the diagnosis of melanoma and nonmelanoma skin neoplasms. However, studies have mostly included heterogenous populations and analyses, potentially providing bias in diagnostic comparisons and rates of unnecessary excisions. Dinnes et al concluded that RCM was promising among equivocal lesions, and despite a generally high sensitivity across studies, there was considerable heterogeneity in specificity and studies were generally at high or unclear risk of both bias and concern regarding applicability. Recommendations for future studies included recruitment of prospective and consecutive participants with equivocal lesions ascertained at dermoscopy, assessed and interpreted by RCM in a standard health care setting within multicenter approach, including systematic follow-up of nonexcised lesions. This prospectively randomized clinical study was designed according to recommendations and proves that, within a homogenous clinical setting, physicians’ diagnostic accuracy is much improved with most melanomas excised at baseline, and those with delayed diagnoses were mainly MIS.

In an era of economic austerity, there is an urgent need for efficient health care services. Ferris suggested that cost-benefit analysis of sophisticated technology should ideally be

---

**Table 3. All Lesions Excised at Baseline and Follow-up With Excision Ratios and NNE**

| Characteristic                | No. (%)          | Standard therapeutic care + RCM | Standard therapeutic care only |
|------------------------------|------------------|--------------------------------|--------------------------------|
| No. of patients              | 3165             | 1583                           | 1582                           |
| Lesions excised              | 2392 (75.6)      | 836 (52.8)                     | 1556 (98.4)                    |
| Melanoma                     | 572 (23.9)       | 278 (33.2)                     | 294 (18.9)                     |
| Malignant, nonmelanocytic    | 53 (2.2)         | 16 (1.9)                       | 37 (2.4)                       |
| Benign, melanocytic          | 1643 (68.7)      | 509 (60.9)                     | 1134 (72.9)                    |
| Benign, nonmelanocytic       | 59 (2.5)         | 17 (2.0)                       | 42 (2.7)                       |
| Benign, inflammatory         | 65 (2.7)         | 16 (1.9)                       | 49 (3.1)                       |
| Positive predictive value    | 23.9             | 33.3                           | 18.9                           |
| Ratio                        |                  |                                |                                |
| Benign to malignant          | 2.8:1.0          | 1.8:1.0                        | 3.7:1.0                        |
| Benign, melanocytic to melanoma | 2.9:1.0        | 1.8:1.0                        | 3.9:1.0                        |
| NNE a                        | 4.2              | 3.0                            | 5.3                            |

---

**Abbreviations:** NNE, number needed to excise; RCM, reflectance confocal microscopy.

---

* NNE was reduced by 43.2% with adjunctive use of RCM.
assessed among high-risk patients randomized to receive intensive vs traditional surveillance. Data from the present study will be applied to an independent, separate cost-benefit analysis in response to this request.

Limitations

This study does not address issues of overdiagnosis associated with early melanoma detection. Furthermore, applicability of this trial is limited to referral centers with RCM experience, but future application of RCM into a general dermatology setting (not specialized clinics) may decrease morbidity among suspect lesions following adequate training. The accuracy analyses related to RCM experience includes a subset of 800 excised lesions with physician name recorded (other data were not recorded). This study does not consider quality of life or reduced surgical waiting lists. Finally, the results of this study cannot be attributed to RCM alone because the patient pathway for those without immediate excision foresaw additional dermoscopy and occasional RCM assessments.

Conclusions

This randomized clinical trial confirms improved physicians’ diagnostic accuracy with adjunctive RCM. Most melanomas are correctly identified at baseline and very few thin melanomas are identified during digital monitoring.

ARTICLE INFORMATION

Accepted for Publication: March 26, 2022.
Published Online: June 1, 2022.
doi:10.1001/jamadermatol.2022.1570
Open Access: This is an open access article distributed under the terms of the CC-BY License. © 2022 Pellacani G et al. JAMA Dermatology.
Author Affiliations: Department of Dermatology, University of Modena and Reggio Emilia, Modena, Italy (Pellacani, Farnetani, Ciardo, Chester, Bassoli, Casari, Pampena, Lai, Longo); Dermatology Clinic, Sapientia University of Rome, Rome, Italy (Pellacani); Department of Surgery, Medicine, Dental Medicine and Morphological Sciences, University of Modena and Reggio Emilia, Modena, Italy (Chester, Kaleci, Stanganelli); Skin Cancer Unit, Istituto Scientifico Romagnolo per lo Studio dei Tumori (IRST) IRCCS, Meldola, Italy (Mazzoni, Pampena, Magi, Mandel); Centro Oncologico ad Alta Tecnologia Diagnostica, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia, Italy (Mirra, Lai, Longo); Dermatology Unit, University of Parma, Parma, Italy (Stanganelli); Center of Research SAVE Study, Milan, Italy (Di Matteo); CEFAT Center of Pharmaceuticals Economics and Medical Technologies Evaluation, University of Pavia, Italy (Colombo).

Author Contributions: Prof Pellacani had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Profs Stanganelli and Longo contributed equally to this work.

Concept and design: Pellacani, Chester, Longo.
Analysis, acquisition, or interpretation of data: Farnetani, Ciardo, Chester, Kaleci, Mazzoni, Bassoli, Casari, Pampena, Mirra, Lai, Mandel, Di Matteo, Colombo, Stanganelli, Longo.
Drafting of the manuscript: Pellacani, Chester, Kaleci, Pampena, Mandel, Longo.
Critical revision of the manuscript for important intellectual content: Pellacani, Farnetani, Ciardo, Chester, Mazzoni, Bassoli, Casari, Mirra, Lai, Mandel, Di Matteo, Colombo, Stanganelli, Longo.
Statistical analysis: Chester, Kaleci, Di Matteo, Colombo.
Obtained funding: Pellacani.
Administrative, technical, or material support: Pellacani, Ciardo, Chester, Mazzoni, Bassoli, Mirra, Lai, Mandel, Stanganelli.
Supervision: Pellacani, Farnetani, Stanganelli, Longo.
Conflict of Interest Disclosures: None reported.

Funding/Support: The Italian Ministry of Health supported this research.
Role of the Funder/Sponsor: The Italian Ministry of Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 2.

REFERENCES

1. Moloney FJ, Guitera P, Coates E, et al. Detection of primary melanoma in individuals at extreme high risk: a prospective 5-year follow-up study. JAMA Dermatol. 2014;150(8):819-827. doi:10.1001/jamadermatol.2014.514
2. Argenziano G, Soyer HP. Dermoscopy of pigmented skin lesions—a valuable tool for early diagnosis of melanoma. Lancet Oncol. 2001;2(7):443-449. doi:10.1016/S1470-2045(01)00422-8
3. Xiong YQ, Ma SJ, Mo Y, Huo ST, Wen YQ, Chen Q. Comparison of dermoscopy and reflectance confocal microscopy for the diagnostic accuracy of malignant skin tumours: a meta-analysis. J Cancer Res Clin Oncol. 2017;143(9):1627-1635. doi:10.1007/s00432-017-2391-9
4. Braga JC, Scope A, Klaz I, et al. The significance of reflectance confocal microscopy in the diagnosis of solitary pink skin lesions. J Am Acad Dermatol. 2009;61(2):230-241. doi:10.1016/j.jaad.2009.02.036
5. Argenziano G, Cerone L, Zalaudek I, et al. Accuracy in melanoma detection: a 10-year multicenter survey. J Am Acad Dermatol. 2012;67(1):54-59. doi:10.1016/j.jaad.2011.07.019
6. Petty AJ, Ackerson B, Garza R, et al. Meta-analysis of number needed to treat for diagnosis of melanoma by clinical setting. J Am Acad Dermatol. 2020;82(5):1158-1165. doi:10.1016/j.jaad.2019.12.063
7. Salemni G, Teran T, Puig S, et al. Meta-analysis of digital dermoscopy follow-up of malignant skin lesions: a study on behalf of the International Dermoscopy Society. J Eur Acad Dermatol Venereol. 2013;27(7):805-814. doi:10.1111/jdv.12032
8. Condorelli AG, Farnetani F, Ciardo S, et al. Dynamic dermoscopic and reflectance confocal microscopic changes of melanocytic lesions excised during follow-up. J Am Acad Dermatol. 2022;86(5):1049-1057. doi:10.1016/j.jaad.2021.03.081
9. Longo C, Zalaudek I, Argenziano G, Pellacani G. New directions in dermatopathology: in vivo confocal microscopy in clinical practice. Dermatol Clin. 2012;30(4):799-814. doi:10.1016/j.derclin.2012.06.012
10. Pellacani G, Guitera P, Longo C, Avramidis M, Seidenari S, Menzies S. The impact of in vivo reflectance confocal microscopy for the diagnostic accuracy of melanoma and equivocal melanocytic lesions. J Invest Dermatol. 2001;127(12):2759-2765. doi:10.1046/j.jid.7.500993
11. Guitera P, Menzies SW, Longo C, Cesinaro AM, Scolyer RA, Pellacani G. In vivo confocal microscopy for diagnosis of melanoma and basal cell carcinoma using a two-step method: analysis of 710 consecutively clinically equivocal cases. J Invest Dermatol. 2010;130(8):2080-2091. doi:10.1038/jid.2010.84
12. Guitera P, Pellacani G, Crotty KA, et al. The impact of in vivo reflectance confocal microscopy on the diagnostic accuracy of lentigo maligna and equivocal pigmented and nonpigmented macules of the face. J Invest Dermatol. 2010;130(8):2080-2091. doi:10.1038/jid.2010.84
13. Guitera P, Pellacani G, Longo C, Seidenari S, Avramidis M, Menzies SW. In vivo reflectance confocal microscopy enhances secondary evaluation of melanocytic lesions. J Invest Dermatol. 2009;129(1):131-138. doi:10.1038/jid.2008.193
14. Dinnes J, Deeks JJ, Saleh D, et al. Cochrane Skin Cancer Diagnostic Test Accuracy Group. Reflectance confocal microscopy for diagnosing cutaneous melanoma in adults. Cochrane Database Syst Rev. 2018;12(12):CD013190. doi:10.1002/14651858.CD013190
15. Scope A, Farnetani F, Haupt S, Schechtman E, Longo C, Pellacani G. Dermoscopic and clinical predictors of reflectance confocal microscopy patterns of typical nevi on the back and legs: a cross-sectional study. J Am Acad Dermatol. 2021;85(5):1240-1247. doi:10.1016/j.jaad.2020.06.020
16. Gordon LG, Rowell D. Health system costs of skin cancer and cost-effectiveness of skin cancer prevention and screening: a systematic review. Eur J Cancer Prev. 2015;24(2):141-149. doi:10.1097/CEJ.0000000000000056
17. Pezzini C, Kaleci S, Chester J, Farnetani F, Longo C, Pellacani G. Reflectance confocal microscopy diagnostic accuracy for malignant melanoma in different clinical settings: systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2020;34(10):2268-2279. doi:10.1111/jdv.16248
18. Yélamos O, Manubens E, Jain M, et al. Improvement of diagnostic confidence and management of equivocal skin lesions by integration of reflectance confocal microscopy in daily practice: prospective study in 2 referral skin cancer centers. J Am Acad Dermatol. 2020;83(4):1057-1063. doi:10.1016/j.jaad.2019.05.101
19. Pellacani G, Pepe P, Casari A, Longo C. Reflectance confocal microscopy as a second-level examination in skin oncology improves diagnostic accuracy and saves unnecessary excisions: a longitudinal prospective study. Br J Dermatol. 2014;171(5):1044-1051. doi:10.1111/bjd.13148
20. Pellacani G, Farnetani F, Chester J, et al. Cutaneous melanoma systematic diagnostic workflows and integrated reflectance confocal microscopy assessed with a retrospective, comparative longitudinal (2009-2018) study. Cancers (Basel). 2022;14(3):838. doi:10.3390/cancers14030838
21. Witkowski AM, Łudzik J, Arginelli F, et al. Improving diagnostic sensitivity of combined dermoscopy and reflectance confocal microscopy imaging through double reader concordance evaluation in telemedicine settings: a retrospective study of 1000 equivocal cases. PLoS One. 2017;12(11):e0187748. doi:10.1371/journal.pone.0187748
22. Pellacani G, Witkowski A, Cesinaro AM, et al. Cost-benefit of reflectance confocal microscopy in the diagnostic performance of melanoma. JEur Acad Dermatol Venereol. 2016;30(3):413-419. doi:10.1111/jdv.13408
23. Carl P, De Giorgi V, Chiarugi A, et al. Effect of lesion size on the diagnostic performance of dermoscopy in melanoma detection. Dermatology. 2008;206(4):292-296. doi:10.1159/000169939
24. Nelson KC, Swetter SM, Saboda K, Chen SC, Curiel-Lewandrowski C. Evaluation of the number-needed-to-biopsy metric for the diagnosis of cutaneous melanoma: a systematic review and meta-analysis. JAMA Dermatol. 2019;155(10):1167-1174. doi:10.1001/jamadermatol.2019.1514
25. Guitera P, Menzies SW, Coates E, et al. Efficiency of detecting new primary melanoma among individuals treated in a high-risk clinic for skin surveillance. JAMA Dermatol. 2021;157(5):521-530. doi:10.1001/jamadermatol.2020.5651
26. Privalle A, Havighurst T, Kim K, Bennett DD, Xu YG. Number of skin biopsies needed per malignancy: comparing the use of skin biopsies among dermatologists and nondermatologist clinicians. J Am Acad Dermatol. 2020;82(1):110-116. doi:10.1016/j.jaad.2019.08.012
27. Vestergaard ME, Macaskill P, Holt PE, Menzies SW. Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: a meta-analysis of studies performed in a clinical setting. Br J Dermatol. 2008;159(3):669-676. doi:10.1111/j.1365-2133.2008.08713.x
28. Reiter O, Mimouni I, Gdalevich M, et al. The diagnostic accuracy of dermoscopy for basal cell carcinoma: a systematic review and meta-analysis. J Am Acad Dermatol. 2019;80(5):1380-1388. doi:10.1016/j.jaad.2018.12.026
29. Xiong YD, Ma S, Li X, Zhong X, Duan C, Chen Q. A meta-analysis of reflectance confocal microscopy for the diagnosis of malignant skin tumours. J Eur Acad Dermatol Venereol. 2016;30(8):1295-1302. doi:10.1111/jdv.13712
30. Lan J, Wen J, Cao S, et al. The diagnostic accuracy of dermoscopy and reflectance confocal microscopy for amelanotic/hypomelanotic melanoma: a systematic review and meta-analysis. Br J Dermatol. 2020;183(2):210-219. doi:10.1111/bjd.18722
31. Ferris LK. Early detection of melanoma: rethinking the outcomes that matter. JAMA Dermatol. 2021;157(5):511-513. doi:10.1001/jamadermatol.2020.5650
32. Welch HG, Mazer BL, Adamson AS. The rapid rise in cutaneous melanoma diagnoses. N Engl J Med. 2021;384(4):72-79. doi:10.1056/NEJMoa191760
33. Rubin R. Melanoma diagnoses rise while mortality stays fairly flat, raising concerns about overdiagnosis. JAMA. 2020;323(15):1429-1430. doi:10.1001/jama.2020.2669