ORIGINAL ARTICLE

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Line-field confocal optical coherence tomography, a novel non-invasive tool for the diagnosis of onychomycosis

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Summary

Background and objectives: Onychomycosis is common and important to distinguish from other nail diseases. Rapid and accurate diagnosis is necessary for optimal patient treatment and outcome. Non-invasive diagnostic tools have increasing potential for nail diseases including onychomycosis. This study evaluated line-field confocal optical coherence tomography (LC-OCT) as a rapid non-invasive tool for diagnosing onychomycosis as compared to confocal laser scanning microscopy (CLSM), optical coherence tomography (OCT), and conventional methods.

Patients and Methods: In this prospective study 86 patients with clinically suspected onychomycosis and 14 controls were examined using LC-OCT, OCT, and CLSM. KOH-preparation, fungal culture, PCR, and histopathology were used as comparative conventional methods.

Results: LC-OCT had the highest sensitivity and negative predictive value of all methods used, closely followed by PCR and OCT. Specificity and positive predictive value of LC-OCT were as high as with CLSM, while OCT scored much lower. The gold standard technique, fungal culture, showed the lowest sensitivity and negative predictive value. Only PCR and culture allowed species differentiation.

Conclusions: LC-OCT enables quick and non-invasive detection of onychomycosis, with advantages over CLSM and OCT, and similar diagnostic accuracy to PCR but lacking species differentiation. For accurate nail examination, LC-OCT requires well-trained and experienced operators.

KEYWORDS
CLSM, LC-OCT, nail disorders, non-invasive diagnostics, OCT, Onychomycosis

INTRODUCTION

Nail diseases are common and often quite troublesome for the patient.[1] Accounting for nearly 50% of all nail diseases,[2] onychomycosis is widespread, but sometimes difficult to distinguish from other nail disorders like psoriasis, lichen planus, eczematous nails, or onychodystrophy.[1,3] Patients with onychomycosis are prone to additional infectious diseases near the affected site (e.g. erysipelas)[4–6] and can suffer from psychological distress due to physical appearance, nail dystrophy, and pain.[7,8] Accurate diagnosis is essential for optimal treatment, improving patient quality of life and minimizing healthcare costs.[9,10]

The last two authors contributed equally to this work.

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Potassium hydroxide (KOH) preparation, dermatophyte culture, histopathology with periodic acid-Schiff reaction (PAS)-staining, and polymerase chain reaction (PCR) are the standard methods for diagnosing onychomycosis.[11] However, each method has weaknesses regarding sensitivity, specificity, time exposure, invasiveness, and costs.[1,12]

Non-invasive diagnostic tools such as video dermatoscopy (VDS), confocal laser scanning microscopy (CLSM) and optical coherence tomography (OCT) have become increasingly important in the diagnosis of onychomycosis.[1,13–16] In recent investigations, our study group has found that line-field confocal optical coherence tomography (LC-OCT) also shows potential for the in-vivo diagnosis of nail conditions including onychomycosis. Advantages of imaging tools over conventional methods are the possibility to obtain quick real-time images of the entire nail and avoid nail sampling to support the diagnosis. LC-OCT appears promising for diagnosing onychomycosis as it combines the advantages of CLSM and OCT resulting in high cellular resolution combined with penetration depth and the generation of 3D nail-plate images.[17] This study evaluates the sensitivity, specificity, positive and negative predictive values, functionality, and efficiency of LC-OCT for the diagnosis of onychomycosis as compared to CLSM, OCT, and current gold standard methods (KOH-preparation, fungal culture, and PCR) of diagnosis.

PATIENTS AND METHODS

Patients

The study included 100 patients observed at the Department of Dermatology and Allergy of the Ludwig Maximilian University Hospital in Munich, Germany. Figure 1 shows the patient distribution in each group (onychomycosis vs. control). There were no limitations in age or gender. Inclusion in the study required an ongoing, clinically or dermoscopically apparent nail condition and good quality CLSM, OCT, and LC-OCT images. Patients with systemic or topical antimycotic therapy within 3 months prior to inclusion were excluded.

In the onychomycosis group, 48 patients showed onychomycosis of toenails and three patients had affected fingernails. The observed subtypes of onychomycosis[18,19] were distal and lateral subungual onychomycosis (DLSO, 57%), totally dystrophic (33%) and mixed pattern (DLSO and superficial, 10%) onychomycosis.

Study approval was granted by the local ethics committee of the university hospital (Ref.-Nr. 17–699) and each patient gave written informed consent before inclusion. The study was conducted in accordance with the Declaration of Helsinki and international guidelines for human studies.

Methods

First, dermatoscopic images of the nail plate were collected with video dermatoscopy (FotoFinder®, FotoFinder Systems GmbH, Bad Birnbach, Germany). Macroscopic and microscopic high-resolution images of the nail were taken using optical magnification of 20x to 140x. The images were examined for typical dermatoscopic signs of onychomycosis such as white to yellow discoloration, subungual keratosis, onychodystrophy and onycholysis, jagged edges with spikes at the proximal edge of the lesion and/or longitudinal striae.[13,14]

Following dermatoscopy, the nail plate was imaged using CLSM, OCT, and LC-OCT. Table 1 summarizes the device characteristics (resolution, penetration depth, image sizes, and other details) for each method.

1. CLSM was conducted with the VivaScope® 3000 Multiwave handheld device with 830 nm diode laser in reflection mode. Clinically suspicious nail areas were scanned horizontally to the nailbed using the "VivaStacks" function. The sample was considered positive for onychomycosis when observing bright, hyper-reflective filamentous structures or spore-like aggregates, as seen in histopathology.
2. OCT was conducted with the VivoSight Dx™ System, which generates vertical images of the nail plate. The sample was considered positive for onychomycosis when bright, hyper-reflective filamentous structures or spore-like aggregates were seen.
3. LC-OCT was conducted with the deepLive™ System. Each nail was imaged using the vertical (en-coupe), horizontal (en-face) and 3D modalities of the device. Bright, hyper-reflective filamentous structures with "fuzzy" appearance, which interrupted the normal, homogenous integrity of the nail plate were regarded as fungal hyphae. Such streaks typically extended across multiple levels of the nail plate and were often accompanied by visible clefts due to nail destruction.

All images were analyzed by two examiners, experienced in non-invasive imaging as well as in dermatological nail diseases, who agreed on the outcome for each patient.

After non-invasive imaging, a nail sample was obtained and analyzed using:

1. KOH-preparation and direct microscopy: The nail sample was clarified and stained with a solution comprising 90 mL 7.5% potassium hydroxide (KOH), 10 mL DMSO and 120 mg Chlorazol black E. Incubation time was between 2 and 10 minutes. The sample was subsequently examined under a light microscope for (pseudo-)hyphae using 200x magnification.
2. Fungal culture: Kimmig fungal agar (suitable for dermatophytes and yeast) was used for cultivation of fungi. The sample was placed onto the agar with 50 mg/l

FIGURE 1 Flowchart showing patient distribution in the onychomycosis and control group, including number of patients, age-range, mean age and percentage of males and females in each group.
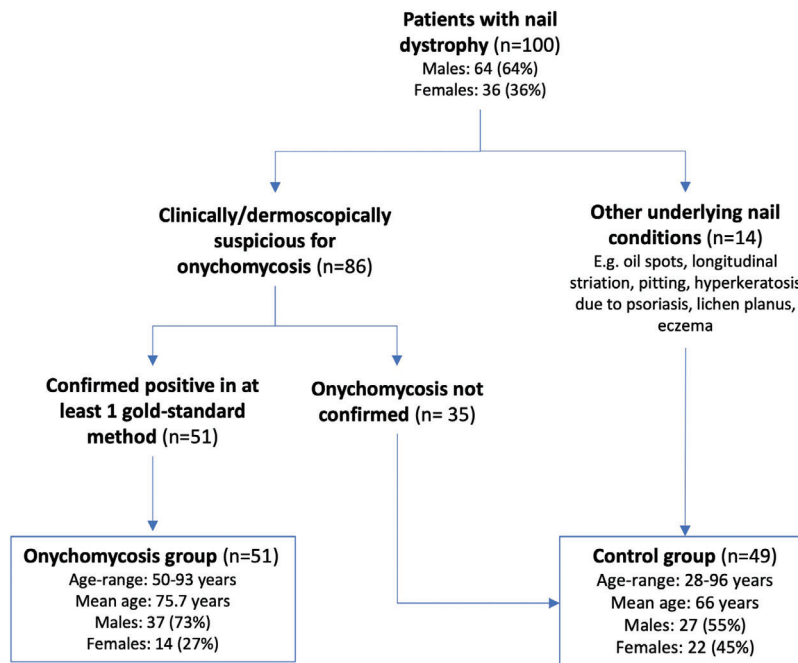

Patients with nail dystrophy (n=100)
Males: 64 (64%)
Females: 36 (36%)

Clinically/dermoscopically suspicious for onychomycosis (n=86)

Other underlying nail conditions (n=14)
E.g. oil spots, longitudinal striation, pitting, hyperkeratosis due to psoriasis, lichen planus, eczema

Confirmed positive in at least 1 gold-standard method (n=51)

Onychomycosis not confirmed (n= 35)

Onychomycosis group (n=51)
Age-range: 50-93 years
Mean age: 75.7 years
Males: 37 (73%)
Females: 14 (27%)

Control group (n=49)
Age-range: 28-96 years
Mean age: 66 years
Males: 27 (55%)
Females: 22 (45%)

TABLE 1 Device and measurement characteristics for LC-OCT, OCT and CLSM.

Method	Device	Manufacturer	Resolution (μm)	Penetration depth in nails (μm)	Images/field of view	Other details
CLSM	VivaScope® 3000 Multiwave	VivaScope GmbH, Munich, Germany	1.25–5	400–500	0.75×0.75 mm² at 6.5 μm depth intervals	Immersion oil and ultrasound gel application between the device probe and nail surface for better index matching
OCT	VivoSight DX™ System	Michelson Diagnostics Ltd, Maidstone, Kent, UK	7.5–10	1500	6×6 mm²	No index-matching fluid is required, just an appropriately selected plastic spacer for the handheld probe to ensure that the nail is put into focus.
LC-OCT	deepLive™ System	DAMAE Medical, Paris, France	1.1–1.3	500	1.2×0.5 mm² (2D vertical and horizontal mode) 1.2×0.5×0.5 mm³ (3D mode)	Immersion oil was applied between the glass window of the device and the nail surface for better index matching.

Abbr.: CLSM, confocal laser scanning microscopy; OCT, optical coherence tomography; LC-OCT, line-field confocal optical coherence tomography

chloramphenicol and left to incubate for 3 weeks at 28°C. The plate was scanned weekly for fungus growth. Species differentiation was performed in positive cases, based on the presence of specific morphological features.

3. PCR: DNA extraction from the sample was performed using the QIAamp DNA Mini Kit (ID:51304, Qiagen, Hilden, Germany), yielding DNA sized up to 50 kb. PCR was subsequently performed with EUROArray Dermatomycosis (EUROIMMUN Medizinische Labordiagnostika AG, Lübeck, Germany), which amplified specific gene regions of pathogens in a multiplex procedure. Annealing temperature was 55°C. The PCR products were fluorescently labelled and hybridized to corresponding probes on biochip microarray slides. Detection and evaluation of amplified DNA products was performed with the proprietary software, warranting objective result reliability.[20]

PCR was not done for four patients due to cost restrictions. In these cases, histopathology was performed:

TABLE 2 Overview of the results for each diagnostic method including the total number of positive results, the sensitivity, specificity, PPV, and NPV.

	Positive result (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
LC-OCT (n = 100)	58	92.2	77.6	81	90.5
OCT (n = 100)	69	86.3	49	63.8	77.4
CLSM (n = 100)	49	78.4	81.6	81.6	78.4
PCR (n = 93)	46.2	87.8	100	100	88
Culture (n = 98)	13.3	26	100	100	56
Native/KOH (n = 98)	37.8	74	100	100	79

Abbr.: PPV, positive predictive value; NPV, negative predictive value; LC-OCT, line-field confocal optical coherence tomography; CLSM, confocal laser scanning microscopy; OCT, optical coherence tomography; PCR, polymerase chain reaction; KOH, Potassium hydroxide

1. Histopathology with PAS staining: Sampled nail material was embedded in paraffin, stained using PAS reaction and analyzed microscopically.

Statistical Analysis

Sensitivity, specificity, negative and positive predictive values were calculated for each diagnostic method, except for histopathology as it was only performed in four patients.

Sensitivity, defined as the percentage of true positives, demonstrated how well a method could detect onychomycosis in affected patients. Specificity, defined as the percentage of true negatives, determined how accurately the technique could identify patients without fungal infection. The positive predictive value (PPV) indicated the probability that a patient with a positive test result truly had onychomycosis. The negative predictive value (NPV) represented the probability that a patient with a negative test result did not have onychomycosis. KOH-preparation, fungal culture, PCR or histopathology were used as benchmark and gold standard. A positive finding in any of the four confirmed the diagnosis of onychomycosis, as not all methods could be performed for every patient.

RESULTS

Table 2 summarizes the total number of positive results, sensitivity, specificity, PPV, and NPV of each method, excluding histopathology.

Sensitivity

LC-OCT achieved the highest sensitivity (92.2%), followed by PCR (87.8%), OCT (86.3%), CLSM (78.4%), KOH-preparation (74%), and fungal culture (26%) (Table 2).

Specificity

PCR, fungal culture, histopathology, and KOH-preparation were taken as gold standard methods for onychomycosis, which implied a specificity of 100%. Compared to the gold standard techniques, CLSM had the highest specificity (81.6%), followed by LC-OCT (77.6%), and OCT (49%) (Table 2).

The non-invasive imaging techniques LC-OCT, OCT, and CLSM were compared with each other and gold standard methods. Positive and negative correlations between the diagnostic methods for onychomycosis are also discussed.

LC-OCT

LC-OCT showed positive results in 58% of all tests conducted (58/100), higher than the average of all methods (46%). 81% (47/58) of the positive results were found in the onychomycosis, 19% (11/58) in the control group. Figure 2 shows exemplary images in vertical, horizontal, and three-dimensional mode.

LC-OCT offered the highest sensitivity of all tested methods (92.2%) and high specificity (77.6%). PPV and NPV were 81% and 90.5% respectively, resulting from a high level of true positives and negatives. Notably, LC-OCT had better sensitivity (92.2%) and NPV (90.5%) than the gold standard methods, although closely followed by PCR (sensitivity 87.8%, NPV 88.8%). The other gold standard methods had considerably lower sensitivities and NPVs than LC-OCT (Table 2). The sensitivity of LC-OCT was also higher than the other non-invasive techniques but closely followed by OCT (sensitivity 86.3%). CLSM ranked third in sensitivity (78.4%).

The NPV of LC-OCT (90.5%) was considerably higher than OCT (77.4%) and CLSM (78.4%). LC-OCT specificity (77.6%) and PPV (81%) were lower than the gold standard methods,
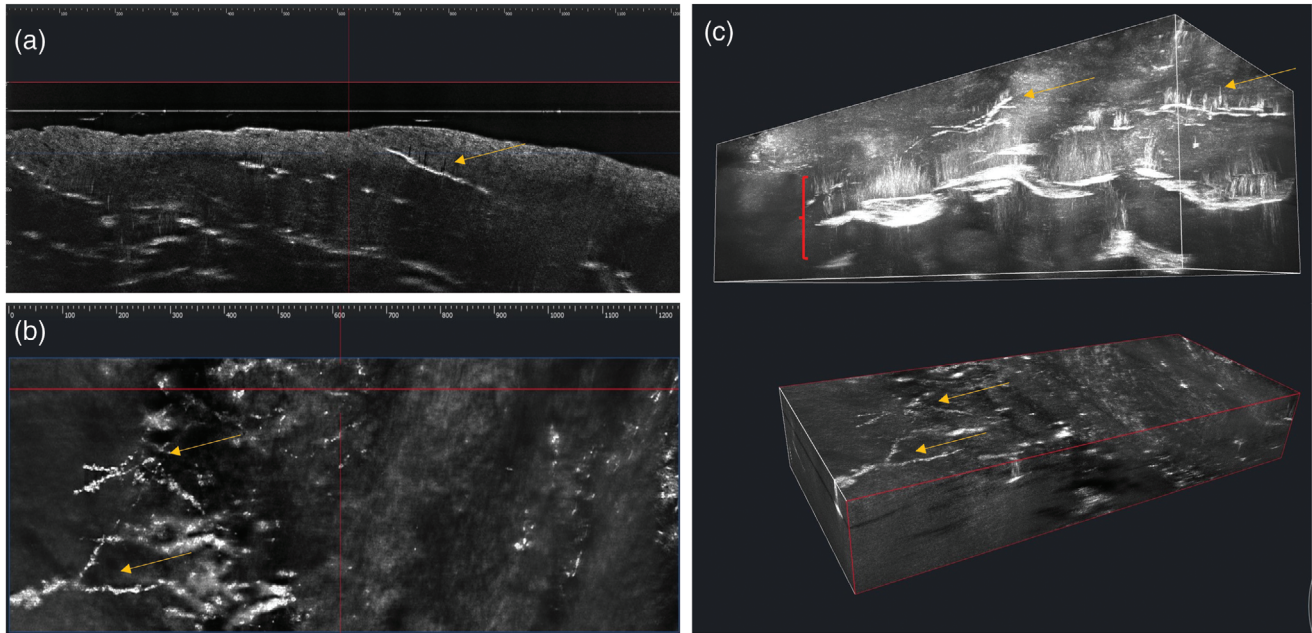
FIGURE 2 Onychomycosis in LC-OCT: (a) vertical (b) horizontal (depth: 250 μm) and (c) 3D LC-OCT images showing a nail plate affected by onychomycosis. The hyphae are visible as hyper-reflective thin, branching structures spanning multiple layers of the nail plate (yellow arrows). Nail destruction and clefting can also be seen surrounding the hyphae (red bracket). (LC-OCT, DAMAE medical, 2D images: 1.2×0.5 mm^2, 3D images: 1.2×0.5×0.5 mm^3)

FIGURE 3 Onychomycosis in CLSM. (a, b) Horizontal CLSM images showing hyper-reflective thin filamentous hyphae (yellow arrows), as well as slightly thicker and rounder spore-like aggregates with a similar presentation as in histopathology (red arrows). (CLSM, VivaScope GmbH, 750×750 μm)
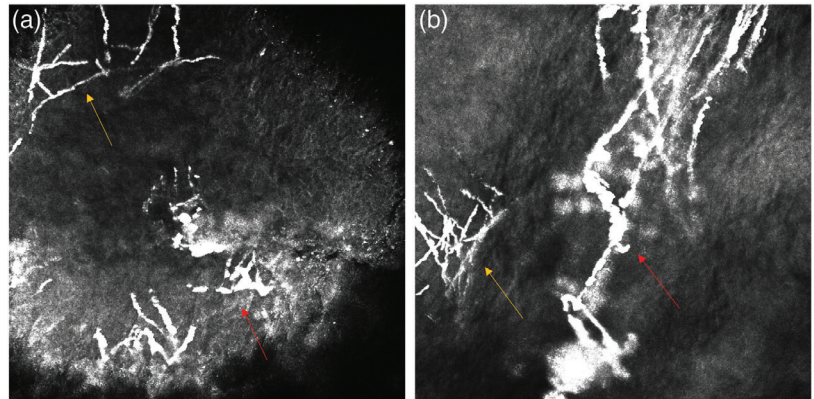
but comparable to CLSM (specificity 81.6%, PPV 81.6%) and much higher than OCT (specificity 49%, PPV 63.8%).

LC-OCT showed the highest positive correlation with OCT (79.5% of patients) and lowest with culture (20.7% of patients). Conversely, the highest negative correlation was seen with culture (92.9% of patients) and lowest with OCT (38% of patients).

CLSM

CLSM showed positive results in 49% of tested patients (49/100), resembling PCR (46.2%) and higher than the average of all methods (46%). 82% (40/49) of the positive results were found in the onychomycosis, 18% (9/49) in the control group. Figure 3 shows exemplary images taken in horizontal mode.

CLSM had a sensitivity of 78.4% and specificity of 81.6%. The PPV and NPV were 81.6% and 78.4% respectively, representing a high number of true positives and negatives. Compared to gold standard methods, the sensitivity of CLSM (78.4%) ranked below PCR (87.8%) but above KOH-preparation (74%) and culture (26%). The NPV of CLSM (78.4%) was below PCR (88.0%) and comparable to KOH-preparation (79%), but clearly above culture (56%).

In specificity, CLSM (81.6%) ranked higher than LC-OCT (77.6%) and OCT (49%). Conversely, CLSM's sensitivity (78.4%) was lower than LC-OCT (92.2%) and OCT (86.3%).
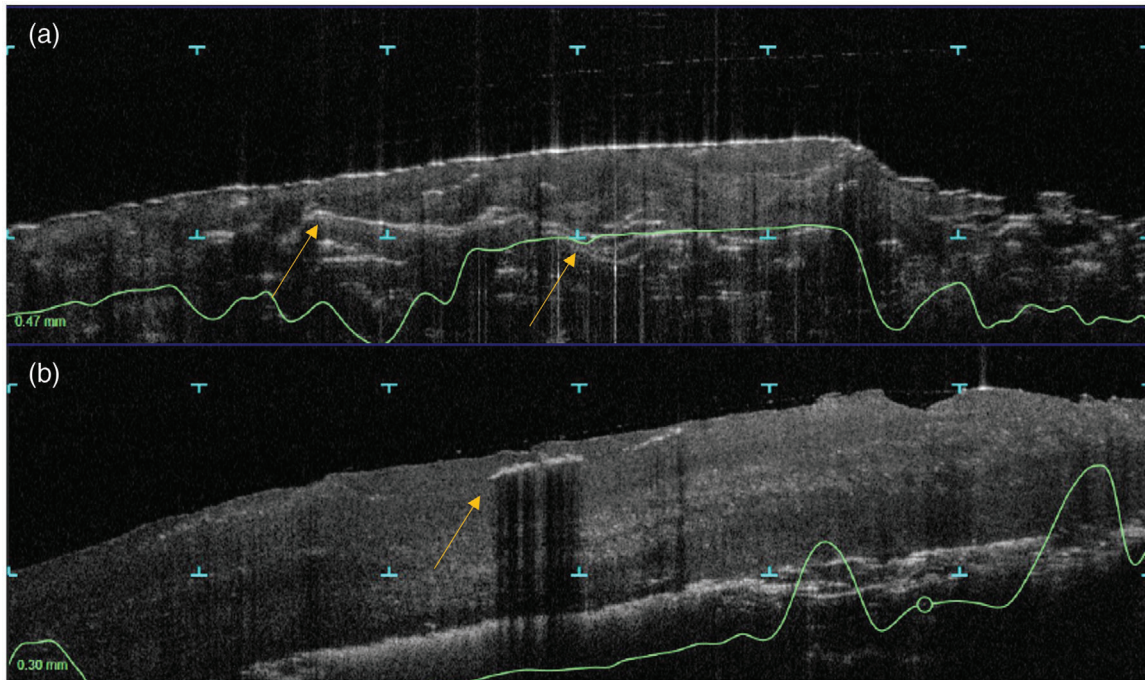
FIGURE 4 Onychomycosis in OCT. (a, b) Vertical OCT images of the nail plate showing hyper-reflective thin filamentous hyphae with a darker hypo-reflective zone underneath (yellow arrows) (OCT, Michelson Diagnostics Ltd, 6×6 mm).

PPV of CLSM (81.6%) was comparable with LC-OCT (81%), but above OCT (63.8%).

In NPV (78.4%), CLSM corresponded with OCT (77.4%) but ranked below LC-OCT (90.5%).

CLSM showed the highest positive correlation with LC-OCT (72.3% of patients) and lowest with culture (20.4% of patients). The negative correlation was highest with culture (92.2% of patients) and lowest with OCT (40% of patients).

OCT

OCT showed positive results in 69% of tested cases (69/100), the highest percentage of all techniques. 64% (44/69) of the positive results were found in the onychomycosis, 36% (25/69) in the control group. Figure 4 shows exemplary OCT images taken in vertical mode.

OCT had high sensitivity (86.3%), but comparably low specificity (49%). PPV (63.8%) and NPV (77.4%) signified a higher proportion of true negatives than true positives. OCT sensitivity (86.3%) was like PCR (87.8%) but higher than KOH-preparation (74%) and fungal culture (26%).

NPV of OCT (77.4%) was lower than PCR (88.0%) and KOH-preparation (79%), but higher than culture (56%).

OCT had the lowest specificity (49%) of all methods tested and lowest PPV (63.8%).

Comparing the non-invasive imaging techniques, OCT had a lower sensitivity (86.3%) than LC-OCT (92.2%), but a higher sensitivity than CLSM (78.4%). NPV of OCT (77.4%)

was comparable to CLSM (78.4%), but clearly below the NPV of LC-OCT (90.5%).

OCT showed the highest positive correlation with LC-OCT (79.5% of patients) and lowest with culture (13% of patients). The highest negative correlation was seen with culture (87.1% of patients) and lowest with LC-OCT (38% of patients).

Differentiation of species

Differentiation of fungal species was possible with PCR and culture in 47 cases. Four different pathogens were identified: *Trichophyton rubrum (TR)*, *Trichophyton interdigitale (TI)*, *Candida parapsilosis (CP)*, and *Candida guilliermondii (CG)*.

Reliable species differentiation was possible in 41 of 43 positive PCR tests. The two cases without species determination were reported to have an infection with dermatophytes but lacked sufficient material for exact classification. *Trichophyton rubrum* was found in 73.2% (30/41), *Trichophyton interdigitale* in 17.1% (7/41), *Candida parapsilosis* in 9.8% (4/41), and *Candida guilliermondii* in 4.9% (2/41) of the positive PCR cases. One patient was identified with both *TR and CG* and one with both *TR and CP*. Fungal culture was positive in only 13 cases. The growth of *TR* was seen in 69.2% (9/13) and *CP* in 30.8% (4/13). LC-OCT detected fungal infection in 32/33 cases of TR, 7/7 cases of TI, 4/5 cases of CP and 2/2 cases of CG.

TABLE 3 Comparison of seven diagnostic methods with regards to the duration until final diagnosis, costs per examination (based on the German medical fee schedule, GOÄ), costs of device acquisition and other resources (such as material and staff) and the possibility of species differentiation.

	Time until final diagnosis	Costs per examination (€)	Device acquisition costs and material/staff	Species Differentiation
KOH preparation	Approx. 30 min	8.04	Low costs, but high staff expertise	No
Culture	3 weeks	16.08	Low costs, but high staff expertise	Yes
Histopathology (PAS staining)	1–2 days	46.92	Low costs, but high staff expertise	No
PCR	1–2 days	113.96	High (material, devices, staff)	Yes
LC-OCT	Approx. 5 min	140	High (device approx. 150,000 €)	No
CLSM	Approx. 10 min	140	High (device 70,000–185,000 €, depending on exact configuration)	No
OCT	Approx. 5 min	80	High (device approx. 85,000 €)	No

Abbr.: KOH, Potassium hydroxide; PCR, polymerase chain reaction; LC-OCT, line-field confocal optical coherence tomography; CLSM, confocal laser scanning microscopy; OCT, optical coherence tomography

Duration, costs, efforts

Table 3 gives an overview of the duration until final diagnosis, costs per examination (based on the German medical schedule of fees, GOÄ) and device acquisition, other resources (such as material and staff), and the ability to differentiate between species for each of the seven diagnostic methods used in this study.

DISCUSSION

This study examined the efficacy of LC-OCT for diagnosing onychomycosis and compared it with existing diagnostic procedures. The typical features of onychomycosis observed with LC-OCT correspond to those reported by Hobelsberger et al. in their pilot case report,[21] while the obtained quantitative results are comparable with the findings reported by Rothmund et al.[1]

Our results confirm previous reports that PCR is an accurate method for diagnosing onychomycosis, even when other gold standard results are negative.[1,22,23] However, all gold standard methods for diagnosing onychomycosis are highly dependent on correct nail sample acquisition (e.g. prior disinfection, obtaining enough material) and expertise in choosing the correct and most affected area.[1,24,25] Nail clippings from unaffected areas or too little material could result in a higher number of false negatives, giving lower sensitivity and NPV. This is not an issue for LC-OCT, OCT and CLSM.

Non-invasive imaging techniques advantageously allow scanning of the entire nail plate. Our findings show, however, that only LC-OCT had a higher sensitivity and NPV than the gold standard methods. This could be because LC-OCT offers three high-resolution imaging modalities (horizontal, vertical and 3D) that allow the most comprehensive real-time analysis of the entire nail to identify fungal hyphae. No reliable statement could be made regarding the sensitivity and NPV of histopathology, as it was only performed in four cases. This limitation can be overcome by incorporating more histopathology examinations to properly compare LC-OCT with histopathology in future research.

LC-OCT specificity and PPV was comparable to that of CLSM, which suggests that both methods are equally effective in correctly identifying negative cases and minimizing false positives. Despite its high sensitivity and NPV, OCT had a rather low specificity and PPV. The OCT device has lower resolution (7.5–10 μm) than both LC-OCT (1.1–1.3 μm) and CLSM (1–3 μm),[17] which makes it more challenging to discern hyphae from other nail conditions and deformations (such as leukonychia) and resulted in a higher number of false positives. The higher penetration depth (1.5 mm) of OCT allowed visualization of the entire nail plate and commonly the transition to the nail bed, even in hyperkeratotic nails. LC-OCT and CLSM were limited by their penetration depths (respectively 500 μm and 250 μm). Future developments of LC-OCT should aim at increasing penetration depth while maintaining the same cellular resolution. This would allow for identification of hyphae deeper in the nail plate even in the presence of hyperkeratosis and further reduce the number of false negatives.

The advantages and disadvantages of the gold standard methods for diagnosing onychomycosis can be found elsewhere.[1,12,14,26,27] In practice, conventional techniques, such as KOH-preparation and fungal culture are often combined in diagnosing onychomycosis. However, LC-OCT, CLSM and OCT are advantageous as they do not require prior nail sampling and the diagnosis can be made by trained medical personnel within only 5–10 minutes, compared to days or even weeks, as for PCR, histopathology, or fungal culture (Table 3). This suggests that patients could receive diagnosis and treatment during a single consultation, saving time and resources. We found that LC-OCT and OCT offer the easiest and quickest handling for scanning nail plates, whereas CLSM took longer and was slightly more challenging without an integrated dermatoscopic camera in the hand-held device for exact navigation on the nail. While some authors state that in vivo CLSM is too

complicated for routine use,[28] Krammer et al. found that *ex vivo* CLSM allows for rapid and accurate detection of onychomycosis, with a sensitivity (91.67%) similar to that of PCR and LC-OCT.[5] However, *ex vivo* CLSM requires prior nail sampling.

A drawback of LC-OCT, CLSM, and OCT is that they, in contrast to PCR and fungal culture, do not enable species identification. The differentiation between species is helpful in choosing correct antimycotic treatment.[4] Culture also indicates pathogen vitality, an important factor to monitor in therapy-resistant cases and recurring disease.[1] This advantage is, however, offset by the relatively low sensitivity (26%). Past studies have confirmed the low sensitivity of culture in diagnosing onychomycosis, although with significant study-to-study variability; Rothmund et al. found a comparable sensitivity (20.5%), whereas other studies range between 30% and 60%.[1,27] It remains unclear as to why the sensitivity found in our study falls in the lower range. Possible explanations could be limited viability of fungal cells, too little sample material for growth in culture or suboptimal sampling locations.[25]

LC-OCT was equally capable of identifying infection caused by *Trichophyton* and *Candida* species, but further studies with a higher number of nails affected by *Candida* should be performed.

Another drawback is the high acquisition cost of the imaging devices (Table 3), also true for LC-OCT. However, the primary reason for acquiring the LC-OCT device is for diagnosing skin tumors such as basal cell carcinoma, for which it has shown high diagnostic accuracy and inter-observer agreement.[29] Onychomycosis is an additional indication for which the device could be used concomitantly.

The handling of OCT, CLSM and LC-OCT requires specialized training and experience on nails. However, the gold standard techniques and laboratory analysis equally require qualified personnel for acquiring correct nail samples (Table 3). Artificial intelligence could potentially be used in the systematic analysis of collected images to support the diagnosis of onychomycosis in the future.

The high number of false negatives and the fact that traditional gold standard methods require accurate nail clippings, create a need for suitable in-vivo approaches for correctly diagnosing onychomycosis to properly treat this common and life-quality impairing nail condition. LC-OCT allows quick and accurate detection of hyperreflective fungal hyphae in nails without the need for nail sampling and should be considered for standard clinical practice. Further studies should investigate how LC-OCT can be used for tracking clinical progress under therapy.

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CONFLICT OF INTEREST
None.

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