Recent Advances in Diagnostic Technologies for Melanoma

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Abstract Melanoma is a malignant tumor occurring typically in the skin. Advanced melanoma has very poor prognosis, and is also called the “king of cancer”. On the other hand, early-stage melanomas are known to be cured completely by relatively simple treatments. Therefore, early detection and treatment of melanomas is very important. However, many melanomas are still diagnosed by subjective evaluation of a physician, in other words, visual inspection. Recently, the demands for development of quantitative melanoma diagnostic technology are increasing. Much research on melanoma diagnosis has progressed in response to these demands. This review introduces some recent advances in melanoma diagnosis using spectral imaging techniques, impedance measurement and diagnostic image analysis, and also briefly describes a novel biological agent against melanoma developed in Japan. A high-quality system using multispectral imaging technique has attracted attention, but the low specificity has been regarded as a problem. It should be noted that descriptions of medical contents are limited because this review is written for engineers and researchers.

Keywords: melanoma, skin, diagnostic technologies, spectral imaging, skin impedance.

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1. Introduction

Skin is an organ that shapes the human body, and plays an important role to isolate the human body from external environment. The skin is roughly divided into an epidermis, corium and subcutaneous tissue. The structure of the epidermis is shown in **Fig. 1**. The epidermis is further subdivided into the horny layer, granular layer, prickle cell layer and basal layer, in descending order from the outermost layer. Among these layers, only cells in the basal layer, which are called basal cells, can divide to form new cells. The newly formed basal cells move upward to the upper layers. This phenomenon is known as ‘turnover’. The barrier function of the skin is maintained by repeated turnover. Generally, cells in the epidermis are completely replaced every 28 days. For more information, refer to a textbook on skin anatomy such as reference [1].

Melanocytes are cells that produce the melanin pigment, and they exist in the basal layer. Normal melanocytes produce eumelanin which is dark brown. On the other hand, a melanocyte that has mutated melanocyte-stimulating hormone (MSH) receptor produces pheomelanin which is reddish brown. More detailed information about melanin production in melanocytes is described elsewhere [2, 3]. Eumelanin plays a role in mitigating damage to genes by absorbing ultraviolet rays. Pheomelanin has little ability to absorb ultraviolet rays. On the contrary, pheomelanin exposed to ultraviolet rays produces oxygen radicals that attacks genes actively [4]. Melanocytes that have become cancerous grow to form a melanoma. Individuals with red hair who produce little eumela-

nin hereditarily have more than three times the risk of developing melanoma than the general population [5]. Blood or urine level of 5-S-cysteinyl-dopa (5-S-CD), a precursor of eumelanin, is utilized as a biomarker for diagnosing melanoma or determining the treatment effect [6]. However, high 5-S-CD levels are only found in advanced melanomas. No biomarker useful for early diagnosis has been discovered. Like many other tumors, a melanoma possesses a characteristic called “diversity”. Many recent biological studies have elucidated that normal cells perform physiological functions as biological tissue in collaboration with neighboring cells. On the other hand, tumor cells behave “selfishly”, expressing abnormal functions and exhibiting abnormal replication. As mentioned above, cancerous melanocytes replicate to form a melanoma. Cancerous melanocytes also produce melanin selfishly. Normal melanocytes produce melanin stably at a uniform density, consequently forming circular, single-colored pigmented skin lesions (PSL). On the other hand, cancerous melanocytes form PSL that are heterogeneous in both color and shape. We call this phenomenon “diversity of a melanoma”. **Figure 2** shows several melanoma pictures recorded in our previous study. These pictures are measured with the protocol approved by Institutional Review Board. As is clear from the figure, the appearance of melanoma differs in each case. Another characteristic of malignant tumors is vascularization. Cancer cells secrete a blood vessel growth factor, generating blood vessels around themselves to obtain nourishment necessary for replication. Therefore, a melanoma attracts blood compared with benign PSLs. In other words, the skin around the melanoma appears redder than normal skin under visible light. Therefore, vascularization also has a tendency to increase the “diversity of a melanoma”.

Melanoma is well known to be a cancer with poor prognosis. According to a previous study [7], advanced melanoma has a poor five-year survival rate of 11%. On the other hand, early melanoma has five-year survival rates as high as 93%, and is one type of cancer that achieves complete cure. The American Joint Committee on Cancer (AJCC) summarized stage classification of the

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Fig. 1 Structure of the epidermis and diagnostic strategy for melanoma.

melanoma in 2002 [8]. The AJCC classification is generally proportional to tumor thickness. Five-year survival rate of melanoma decreases by 30% as the stage advances. Therefore, early detection and early treatment are most important for melanomas.

As another feature of melanoma, regional and ethnic differences in melanoma morbidity rate are very wide indeed. According to one study [9], the Oceania region has the highest morbidity rate of 40 per 100,000 population. Northern European region also has high morbidity rate (10). On the other hand, Asian region has relatively low morbidity rate (0.5). Melanoma patients are increasing all over the world. However, the increase in melanoma

Fig. 2 Example of melanoma pictures.

patients among black people who have a high melanin-producing ability hereditarily has not been confirmed. On the contrary, their melanoma morbidity rate is about one-tenth compared to other races.

Despite this situation, a practical diagnostic method for early detection of melanoma has not been established. Current diagnostic strategy for melanoma is shown in **Fig. 1**. The melanoma is a visible tumor, unlike many other tumors. Therefore, the appearance of the PSL is mainly utilized as the first-line diagnostic strategy. Many doctors still diagnose melanoma by visual inspection with naked eyes. The diagnosis of melanoma is confirmed by biopsy and pathological examination. Diagnosis using equipment called dermoscopy is gaining popularity. The dermoscopy consists of a light source, a polarized plate, and a magnifying glass. The dermoscope is just a magnifying glass specialized for observing PSLs, and it is impossible to determine a diagnosis of melanoma only by dermoscopy. According to a review article [10], a dermatologist using the dermoscope improved the accuracy of melanoma diagnosis by 49%. However, the accuracy of melanoma diagnosis by a physician who is not a dermatologist did not change regardless of the use of a dermoscope.

To overcome the above situation, there is a strong need to diagnose melanomas quantitatively and objectively. In response to such needs, many diagnostic systems utilizing different strategies are being developed in the engineering field as shown in **Fig. 1**. Several diagnostic systems will be introduced and discussed in this paper. Moreover, a novel biological agent against melanoma developed in Japan will also be described briefly.

2. Diagnostic Technologies for Melanoma

As mentioned above, the diagnostic method for melanoma has not been established. Many attempts have been made in the medical, biological and engineering fields to improve the diagnostic accuracy of melanoma. The final goal of these studies was to diagnose melanoma precisely, but few studies succeeded to achieve a diagnostic ability equal to an excellent dermatologist. This paper introduces some recent advances in melanoma diagnosis in

Table 1 Melanoma diagnostic technologies and their performance.

technology	described in	averaged sensitivity	averaged specificity	refs
diagnostic impression (dermoscopy)	Chapter 1	83%	86%	10
multispectral imaging (MelaFind)	Chapter 2.1	98%	10%	14, 15, 16
impedance measurement (Nevisense)	Chapter 2.2	98%	25%	23, 24
Diagnostic image analysis (DermoPerl)	Chapter 2.3	93%	65%	26, 27, 28
hyperspectral imaging (MSI)	Chapter 2.4	96%	87%	19

the engineering field. Those are summarized in **Table 1**. Accurate verification of diagnosis performance requires a large patient sample, because melanoma has high “diversity”. However, it is very difficult to recruit a sufficient number of patients because there is local difference in the incidence of melanoma. During the past several decades, there were very few studies on methods of melanoma diagnosis with an adequate sample size. Under these circumstances, this paper reviews three systems. First, MelaFind was developed in the U.S., and approved by the Food and Drug Administration (FDA). It is the system nearest to clinical application. Next, Nevisense has been studied in a large-scale clinical trial in Europe. Third, a system using image processing will be described. These systems are advancing rapidly by the widespread use of smartphones. Finally, a hyperspectral melanoma diagnosis system, in which the author was involved in development, will be introduced.

2.1 Spectral imaging technologies

Melanoma diagnostic system using spectral imaging technology is ready to be applied to clinical use. Spectral imaging is a technology that measures an object by multiple wavelengths using a combination of spectroscopy or tunable optical filter and optical sensors such as CCD. This technology has been utilized in the field of remote sensing [11]. An example of its application in Landsat 1 launched in 1972 [12]. Spectral imaging is categorized roughly into multispectral imaging and hyperspectral imaging according to the number of wavelengths measured, which are also called “bands”. Although there is no exact definition for the differences between multispectral and hyperspectral imaging, the former has at most several tens of bands, while the later has even more bands. Initially, hyperspectral imaging was also utilized in the field of remote sensing. The airborne visible/infrared imaging spectrometer (AVIRIS) was the first widely used imaging spectrometer developed at the Jet Propulsion Laboratory for remote sensing [13]. Currently, the spectral imaging is used in many fields.

The technology is also used in skin measurement. One of such medical equipment used to assist the diagnosis of melanoma is MelaFind (MELA Sciences, USA), which was approved for educational use by the FDA., and its use is spreading steadily mainly in Europe and the U.S. Because the system is already commercially available, recent reports do not describe in detail how the present system makes a diagnosis. According to an old report, multiple image parameters were calculated from the images of three wavelengths (400, 550, and 700 nm), and 13 parameters with high melanoma diagnosis ability were selected [14]. Then, the linear sum of these 13 parameters was calculated by linear classifier. Malignancy of the PSLs was estimated by the

linear sum. This method was used to examine 76 PSLs including 25 melanomas, with high sensitivity and specificity of 100% and 92%, respectively. A preliminary clinical study using the equipment was reported in 2000 [15], and a large-scale clinical trial enrolling 1,383 patients was reported in 2011 [16]. While high sensitivity of 98.3% (172/175) was reported, specificity was low at 9.9%. This means that 90 of 100 non-melanoma lesions would be identified as melanoma. From these results, some reports warned “MelaFind almost always recommends biopsy” [17].

According to a report that validates the impact of the equipment on the dermatologist’s diagnosis [18], the equipment improved dermatologist’s diagnostic sensitivity from 69% to 94%, and declined specificity from 54% to 40%. These results imply that the equipment reduces false-negative results, but increases the medical cost by the enormous false-positive results. A problem on the dermatologist side was also pointed out. The paper reported that some dermatologists did not follow the information obtained from the equipment and followed their own decision. The equipment still has many problems, but it is clear that the equipment has the highest potential of clinical application. Therefore, dermatologists’ attention and expectation are very high..

2.2 Impedance measurements

Nevisense (SciBase AB, Sweden) is also an equipment with high potential of clinical application. This equipment identifies the melanoma using electrical impedance. As one feels a shock when touching an electrical cable, a human body conducts electricity. The human body has a conductance that originates from cell membrane and a resistance that originates from extracellular fluid. The low frequency characteristics of the human body reflect the extracellular environment, while the high frequency characteristics reflect both intracellular and extracellular environment [19].

A Swedish group attempted to develop a device that measures the cell environment electrically using the above-mentioned theory. They reported the impedance characteristics of the skin and the mouth in 1992 [20] and 1996 [21]. They applied sodium lauryl sulfate (SLS) to the skin. SLS is a surface-active agent, and removes sebum from the skin. They measured the impedance characteristics of the skin and its appearance before and after SLS application and reported that various impedance changes could be used for quantitative evaluation of the skin stimulus. From around 2003, the group attempted to develop a new melanoma diagnostic equipment using the same theory [22]. **Figure 3** shows outline of electrode they developed. They hypothesized that the device is capable of distinguishing the orderly and well-shaped environment of the normal cell from the disordered and heterogeneous environment of the melanoma. In a study of 370 patients with

Fig. 3 (a) Schematic overview of the five-bar electrode. (b) Scanning microscope image of micro-invasive pins. (Skin Research and Technology, Volume 19, Issue 2, pp 75–83).

non-melanoma skin tumors, significant impedance differences were found between the lesions and healthy skin. In 2013, they reported that the system achieved sensitivity as high as 98.1% and specificity as high as 24.5% in a trial of 577 lesions including 103 melanomas [23]. Impedance measurement is generally lower in cost than optical measurement. However, accurate measurement of the skin impedance is very difficult because of the presence of many disturbance factors such as humidity and sunlight. The group also reported that skin impedance fluctuates with the seasons [24]. Furthermore, the device also has relatively low specificity. These issues have to be resolved.

2.3 Diagnostic image analysis

There are also many melanoma diagnostic studies using images measured by dermoscopy, which is being used recently in dermatological clinical medicine. A melanoma diagnosis support system using dermoscopic image is now available on the Internet (<https://dermoscopy.k.hosei.ac.jp/DermoPerl/>). Iyatomi et al. [25] built the site in 2004, which is still in operation. They acquired and analyzed 1,258 dermoscopic images via the site, and achieved high sensitivity and specificity of 85.9% and 86.0%, respectively [26]. First, their system extracts the melanoma area from the image using image analysis methods such as thresholding and clustering. Second, a large number of numerical values related to image analyses, such as border length as well as mean and standard deviation of RGB values, are calculated from the extracted image. Finally, these values are converted to a probabil-

ity of melanoma using a neural network.

According to an article reported in 2008 [27], 428 image parameters were calculated from dermoscopy image, and these parameters were reduced to 198 dimensions using principal component analysis. The malignancy of PSLs was evaluated using ten principal components with high melanoma diagnostic ability selected by linear classifier. Some combinations of principal components such as “the difference of center of mass in the x direction between the original tumor area and the area with intensity lower than a threshold of 80” and “the texture correlation in the tumor area in the vertical direction (90 degree) as measured by a co-occurrence matrix with distance parameter, the half of the major axis length of the tumor object” were able to distinguish melanoma with sensitivity and specificity up to 93% and 65%, respectively. However, it is very difficult to explain which characteristics of the melanoma are reflected by these indexes, and to interpret some values used in defining image features, such as “threshold of 80” and “90 degree”.

When using the image analysis method for melanoma diagnosis, the performance of image analysis influences the diagnostic performance. For example, an image that can be analyzed as planned can be diagnosed accurately. On the other hand, the diagnosis performance using unexpected images tends to deteriorate remarkably. Therefore, caution should be exercised when using the analysis results of these systems for melanoma diagnosis. Diagnostic systems using the neural network also require attention. The diagnostic performance tends to depend on the quality of the datasets for neural network training. In this context, the output for an unknown case that was not included in the training datasets tends to be unstable.

Many “melanoma applications” designed for smartphones have also been developed and already become commercially available [28]. These applications should be used with caution because some of the products are technologically immature or have not cleared ethical standards necessary for clinical application. According to a report that validates the diagnostic performance of several applications [29], tele-dermatology application had the highest diagnostic performance. Tele-dermatology is one type of tele-diagnosis. The image taken by the application is forwarded to a dermatologist automatically, and the diagnosis made by the dermatologist will be sent back later. The performance of the camera on the smartphone was also evaluated in the report. Image quality of the cameras on current smart phones may be adequate for tele-dermoscopy, however it is strongly recommended that only physician-based tele-dermatology applications should be used for the time being. The U.S. FDA has developed a guideline for mobile medical applications [30]. However, the effectiveness of this regulation remains unclear.

2.4 Hyperspectral imaging technologies

Some melanoma diagnostic systems using hyperspectral imaging technique are also being developed. The system developed by the author's group achieved sensitivity and specificity up to 96% and 87%, respectively, in a clinical trial, although the subjects were Japanese only and the number of subjects was small ($n = 132$) [31]. **Figure 4** shows hyperspectral imager, called MSI-03, developed by author's group. The system evaluates the “diversity of a melanoma” using a relatively simple method named “spectral angle and entropy”. Because hyperspectral imaging allows observation

Fig. 4 Hyperspectral imager MSI-03 developed by author's group.

of a target in more detail than multispectral imaging, higher sensitivity and specificity may be achieved with hyperspectral imaging compared to systems using multispectral imaging such as MelaFind. However, a system using hyperspectral imaging tends to be expensive and large by the same reason. However, a system using hyperspectral imaging technologies allows observation of the skin at the pigment molecular level. On the other hand, systems not using hyperspectral imaging technologies, such as multispectral imaging or color imaging, are able to analyze the skin in no more than three or ten colors. Originally, the intensities of these colors are calculated by a diffusion reflection spectrum of the skin. In other words, these colors are obtained from summarized spectra. Because hyperspectral imaging technologies can assess the spectra directly, the skin can be observed in more details. Therefore, melanoma may be distinguished with higher precision using hyperspectral imaging technologies. Another advantage of adopting relatively simple technologies is that system problems can be identified more easily. As mentioned above, melanomas exhibit high diversity and many atypical cases exist. Conventional automatic diagnostic systems calculate many image parameters from patient data, and then use several mathematical methods such as support vector machine to search for the combination of these parameters that most effectively distinguish patient group from non-patient group. Finally, malignancy of the lesion is estimated by a calculated value. Such system is regarded as a so-called "expert system". Some meaningful parameters are often selected as indexes. However, these mathematical methods never select parameters considering the characteristic of the tumor cells. Therefore, the selected parameters do not have biological relevance. In other words, it is very difficult to explain why the selected parameters are useful for the discrimination of melanoma. In the expert system, the relations between patient data and the indexes become a black-box. When a typical case is input for analysis, these systems can distinguish a melanoma with very high precision. However, the precision of these systems for an atypical case declines remarkably. To make matters worse, because of the black-box, the solution to the problems becomes very difficult. Our research group focuses on the diversity in biological characteristics of the tumor cells forming melanomas, and adopts technologies that are able to assess the characteristics (such as color diversity) directly. Therefore, we consider that our system is

able to distinguish a melanoma with high precision while using relatively simple analytical methods. Further developments are anticipated, such as clinical trials in European countries or the U.S. with a high incidence of melanoma, and technological development of small and low-cost systems.

3. Novel Chemotherapeutic Agents against Melanoma

Although this article is written for engineers and researchers who intend to develop new melanoma diagnostic technology, a novel biological agent against melanoma developed in Japan, which has attracted the attention of many dermatologists, should also be introduced briefly. This is a pivotal event in the field of melanoma treatment, and may be a big turning point for melanoma diagnosis. Researchers engaged in studies on melanoma should be aware of this new agent, and reading of references on this agent is highly recommended.

As mentioned above, advanced melanoma of stage IV has poor prognosis. Stage IV patients are generally treated with a combination of surgery, chemotherapy, chemoradiotherapy, and others. The standard therapeutic agent against stage IV melanoma has been ipilimumab, which works to activate the immune system by targeting cytotoxic T-lymphocyte associated protein-4 (CTLA-4). Despite treatment with ipilimumab, the median progression-free survival of stage IV melanoma patients was 2.9 month [32]. Hence, no effective treatment for stage IV melanoma was available. Another novel protein called programmed cell death-1 (PD-1) that acts to activate the immune system was identified in 1992 [33], and an anti-PD-1 monoclonal antibody called nivolumab was developed in 2014. According to the clinical trial result of nivolumab reported in 2015 [32], the median progression-free survival is prolonged to 6.9 month with nivolumab only, and 11.5 month with a combination of nivolumab and ipilimumab. Although the extension of survival is only several months, nivolumab as a novel effective treatment for stage IV melanoma has attracted much attention from dermatologists. If advanced melanomas can be cured completely, the needs for melanoma diagnostic systems would increase more.

4. Conclusion

This article introduces some recent advances in melanoma diagnosis. Because melanomas can be observed by naked eyes, they are the target of research for many researchers. However, like many other cancers, it is very difficult to establish a diagnostic method because of diversity. Moreover, clinical studies of melanomas have to be planned carefully because of the great regional and ethnic differences in melanoma morbidity. Substantial progresses in treatment technology would also influence the needs for diagnostic method. As discussed in this article, current melanoma diagnostic systems have some problems. It is difficult to diagnose melanomas accurately by these systems alone. Currently, these systems are suitable for education purpose or providing additional information for dermatologists on atypical skin lesions. However, there is a strong need for diagnosing melanomas quantitatively and objectively because of the global increase in number of melanoma patients. The author would feel amply rewarded for the efforts if this review proved helpful to melanoma researchers.

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manuscript.

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