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Correlation Analysis of Oral Lesion Sizes by Various Standardized Criteria

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Abstract

Objective—Requirements of an NCI contract examining a novel treatment for leukoplakia were to compare standard bi-dimensional measurement of oral lesions to examine for correlation with Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and to examine the feasibility of digital image analysis for automated measurements.

Study Design—Retrospective review

Methods—We examined 13 patients by bi-dimensional measurement and compared these measurements to 1) RECIST criteria, 2) scalar digital measurements using a standardized measuring device within the photograph, and 3) pixel number.

Results—RECIST criteria correlated (r -squared=0.8535, $p<0.0001$) with bi-dimensional measurements. Digitized measures in photographs correlated with bi-dimensional measurements (r -squared=0.6661, $p=0.0007$), but were time consuming. There was minimal to no correlation between pixel number in Adobe Photoshop and the other measures.

Conclusion—Bi-dimensional measurement of oral leukoplakia and RECIST criteria are highly correlated. Digital photography measurements, though highly correlative, are very cumbersome.

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We recommend bi-dimensional or longest length measurement and a simple photograph as standard of documentation for leukoplakia lesions.

Introduction

As defined by the World Health Organization, oral leukoplakia is a white patch or plaque that cannot be characterized clinically or pathologically as any other disease.¹ It has been identified as a precursor of oral squamous cell carcinoma. The prevalence varies from less than one to more than 5 percent.^{2,3} Leukoplakia is seen most frequently in middle-aged and older men, with an increasing prevalence with age.⁴ It is associated with alcohol and tobacco use and chronic inflammation, although idiopathic forms are not uncommon.⁵ This disease process can occur throughout the oral cavity with the most common sites being the buccal mucosa, alveolar mucosa and lower lip. Lesions of the floor of mouth are at highest risk for malignant or dysplastic change, whereas the lateral tongue and lower lip are also considered high risk sites.⁴ The incidence of malignant transformation has been estimated to range from less than 1 to 17%.^{2,3,5}

Prevention of malignant transformation is particularly important in view of the poor prognosis associated with oral squamous cell carcinoma. Modalities that have been considered for the treatment of oral leukoplakia include observation, surgical resection, and topical or systemic medical therapies;^{2,6} none of which have shown to be effective in preventing malignant transformation.² Leukoplakias are not morbid or lethal in and of themselves, and their risk of transformation is relatively low. However, there is no definitive or reliable method to identify those lesions that will undergo malignant transformation.^{2,6} Thus, proposed treatments should have minimal adverse effects in terms of incidence and severity.²

Additionally, since leukoplakia lesions can have a variety of appearances in terms of hue (amount of leukoplakia and erythroplakia), degree of homogeneity, and thickness, reliable methods of documentation of leukoplakia size and sites of involvement are vital for use as a standard surrogate lesion for any studies. Currently, we are conducting a National Cancer Institute (NCI)-sponsored clinical trial for treatment of oral leukoplakia. This is a phase IIa study that has as its principle objective to assess the clinical efficacy of a PPAR-gamma agonist in the treatment of upper aerodigestive leukoplakia. As part of the NCI contract, we investigated 3 separate modalities of documentation of lesion size to better understand if any method is more easily employed reliably in preneoplastic lesions.

Methods

This study was approved by the University of Minnesota Institutional Review Board and is also in compliance with HIPAA (Health Insurance Portability and Accountability Act) guidelines. Thirteen patients with oral dysplastic leukoplakia were evaluated. Patients were enrolled into the study if they had at least one lesion of histologically dysplastic leukoplakia as determined by biopsy. At the time of enrollment, patients underwent history, physical examination, laboratory testing, lesion evaluation with bi-dimensional measurement, photographic documentation of the lesion and incisional biopsy. The bi-dimensional

measurements were taken with a perioprobe calibration device and the greatest length and width bi-dimensional measurements were recorded by the senior authors. The perioprobe is a standard dental calibration device for the quantitation of gingival crevicular pocket depth for the quantitation of periodontal disease. It is calibrated in at 1mm intervals.

Extreme care was taken not to stretch or distort the mucosa and potentially alter the lesion size. The lesions were measured twice. Photography was performed with a Fuji e510 5 megapixel digital camera. Within each photograph, a perioprobe was also used as a standardized measure. The patients were then treated for 12 weeks with a PPAR-gamma agonist. At the conclusion of the 12 week course of treatment, repeat laboratory testing, lesion evaluation via clinical examination and biopsy, and photographic documentation were performed. (See Figure 1)

Using Adobe Photoshop 7.0, the photographs were analyzed by measuring the lesion within the photo. This was performed by measuring the longest length and width of the lesion and also of the perioprobe specific to each photograph. The actual length of the perioprobe is standard, and thus a conversion factor was determined that was used to convert the size of the lesion in the photograph to actual size. Additionally, the boundary of each lesion was outlined within the Photoshop program tracing function, and the number of pixels that constituted the lesion was recorded. If a patient had more than one lesion, each lesion was treated individually and the value for each lesion was summed to determine the total size.

The data recorded for each patient included bi-dimensional measures of the oral leukoplakia lesion pre- and post-treatment, the dimensions and area of the lesion within the photograph, and the total pixel count of the lesion. (See Table 1) The bi-dimensional measurements taken at the time of clinical examination were compared to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, scalar digital measurements with a standardized measuring device in the photograph, and the number of pixels.

Statistics

Correlational coefficients were determined using the Graph Pad Prism scientific statistics program after fitting the data to a first order linear regression function (Graph Pad Software, Palo Alto, CA). P values less than .05 were considered significant.

Results

Thirteen consecutive patients enrolled to the study were included in this analysis. From the bi-dimensional measurements, by RECIST criteria definition, the longest measurement automatically becomes the one recorded to judge response. Although leukoplakia lesion morphology may range from sizes approximating any shape from a circle to a long ovoid, we found that RECIST criteria correlated significantly ($r^2 = 0.8535$, $p < 0.0001$) with bi-dimensional area measurement of the leukoplakia lesion, a longstanding criteria for tumor size quantitation. (See Table 2 and Figure 2) Next, we compared the bi-dimensional measurements from our physical exams with areas calculated from the digitized measures in photographs. The digitized areas correlated significantly with bi-dimensional measurements ($r^2 = 0.6661$, $p = 0.0007$). (See Table 2 and Figure 3) Next we compared the pixel counts

from the photographs with 1) the bi-dimensional measurements of the physical exam 2) the RECIST criteria, and 3) the calculated areas from the photographs. There was significant but low correlation between the RECIST criteria and pixel count ($r^2 = .3068$, $p = 0.0495$). (See Table 2 and Figure 4) Similarly, there was significant but low correlation between the measurements from the physical examination with pixel count ($r^2 = 0.3711$, $p = 0.0271$). (See Table 2 and Figure 5) There was no correlation between number of pixels in Adobe Photoshop and lesion areas derived from the photographs. ($r^2 = 0.1565$ and $p = 0.5121$). (See Table 2 and Figure 6).

Discussion

There is currently no ideal method of measuring an oral cavity leukoplakia lesion, or for that matter, any cancerous lesion. In an effort to adequately quantify change in tumor size in response to treatment, the World Health Organization in 1979 developed a standardized system that was based on bi-dimensional measurement of solid tumors.⁷ However, difficulty with this system led to the development of the RECIST guidelines for evaluating tumor response. The RECIST system simplified tumor measurement by using only the longest uni-dimensional measurement of a lesion, and for multiple lesions, using the sum of the longest diameters.^{7,8}

To document size and response rate in leukoplakia lesions in this study, bi-dimensional measurements were obtained. Our data confirm that there was a strong correlation between bi-dimensional measurement and uni-dimensional measurements of the RECIST criteria. This data suggests that the use of the RECIST criteria for evaluating oral leukoplakia lesion size may be highly useful. These results are consistent with other studies that have validated the RECIST guidelines for other tumor types.^{7,9,10}

With the continued development of computer and photographic technology, medical documentation will slowly incorporate these forms of media into the medical record. Currently, most digital medical images are used for documentation purposes only. It would seem reasonable that as resolution of images and computer software improve, photographic documentation may enhance and improve lesion analysis, and may eventually have a diagnostic role. Mattsson, et. al. were able to distinguish between lichenoid reactions and homogenous oral leukoplakia using digital photography.¹¹ Each patient in this study had their oral lesion photographed per protocol. In each photograph, a perioprobe was present for measurement purposes. Using the computer software program Adobe Photoshop, the perioprobe was measured because it had to be standardized to each photograph. The dimensions of the lesion were then obtained, and these measurements were compared to the perioprobe measurement. There was good correlation between actual measurement and photographic measurement when the perioprobe was used. This, however, was a very cumbersome and time consuming process. Approximately one hour was spent on each photograph to obtain these measurements.

To obtain the pixel count, the entire leukoplakia lesion was outlined with the lasso tool. The Adobe Photoshop program provided the total number of pixels within the outlined boundaries. These were recorded and then statistically compared to bi-dimensional

measurements and photographic measurements. There was minimal to no correlation among these variables, and this was likely due to several difficulties encountered during this process. When taking photos within the oral cavity, the saliva and smooth, shiny surface of the mucosa provide a medium for light reflection, making it difficult to absolutely determine the boundaries of some of the lesions. Conversely, because of oral cavity anatomy, there were areas of darkness or shadow which, again, convoluted the boundaries of some of the lesions.

Obtaining a high quality photographic image is dependent on numerous variables, many of which are specific to the camera. However, environment and subject are also part of the equation. Lighting, distance to the subject, and the location of the subject will affect the quality of a photograph. In this study, there was no standardization of lighting or distance from lens-to-subject. Additionally, the three-dimensional nature of the oral cavity was difficult to capture in a two-dimensional photograph in spite of great care to photograph the lesions in their entirety at a 90 degree angle to the lesions. Lesions that were significantly posterior posed a challenge to photograph, and the more posterior aspect of the lesion often appeared truncated or foreshortened in the photograph. Pixel count in a defined area will be different for each photograph if the above variables are not standardized. This may be possible for certain anatomic sites (e.g. buccal mucosa), but cannot be standardized across anatomic sites.

Thus, our data indicate that bi-dimensional measurement and longest uni-dimensional measurement are sufficient tools for assessing oral leukoplakia size, and resultantly response to treatment. The photographs of the lesions provided superior documentation of lesion appearance, but were unable to be used for measurement purposes. It would be almost impossible to position a patient and camera in the exact same position for photo documentation at different clinical visits. However, future imaging or scanning capabilities may be able to account for current photography variables and create an image that is accurate to size and may also provide three-dimensional information.

Conclusion

We conclude that bi-dimensional measurement of oral leukoplakia and RECIST criteria are highly correlated. We also conclude that digital photography and measurements, though highly correlative, are very cumbersome. We recommend simple bi-dimensional or longest length measurement using a perioprobe with a simple photograph as a standard of documentation for leukoplakia lesion size. We strongly feel that the photograph is useful for simple photo documentation purposes and to help judge lesion heterogeneity, but not for quantitation.

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Figure 1.
Photograph of Leukoplakia Lesion During Measurement

Figure 2.
Measured Lesion Area vs. Longest Measured Side

Figure 3.
Measured Lesion Area vs. Area of Lesion in Photograph

Figure 4.
Longest Measured Side vs. Pixel Count

Figure 5.
Measured Lesion Area vs. Pixel Count

Figure 6.
Area of Lesion in Photograph vs. Pixel Count

Table I

Definitions of Terminology

Measured Lesion Area	Measurement obtained at the time of physical examination using the perioprobe by multiplying longest length and width
Longest Measured Side	Longest measured side of the lesion obtained at the time of physical examination using the perioprobe
Area of Lesion in Photograph	Measurement obtained from a photograph by measuring the length of the perioprobe in the photo and also measuring the length and width of the lesion in the photo. The perioprobe's actual length was known and was used to convert a measurement in the photo to an "actual" measurement. Area was determined by multiplying the calculated length and width
Pixel Count	The number of pixels within the outlined borders of the lesion.

Table 2

Quantitative Data for Leukoplakia Lesions

Patient	Measured Lesion Area	Longest Measured Side	Picture Area	Pixel Count
1	72	9	61.8	18954.67
2	45	9	50.4	33383.33
3	204	17	94	9151.667
4	40	10	75.7	18988.67
5	75	15	122.2	41781.33
6	44	11	68	58757.33
7	78	13	72.6	11475.67
8	300	20	674.6	23445
9	88	11	73.2	91439.67
10	24	11	115.3	34205.67
11	247	19	265.5	168098
12	729	27	586.7	153556.3