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Retrospective Study

Computer-aided clinical image analysis as predictor of sentinel lymph node positivity in cutaneous melanoma.

Digital image processing and SLN+ positivity.

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Abstract

BACKGROUND

Delays in sentinel lymph node biopsy may affect the positivity of non-sentinel lymph nodes. For these reasons, effort is being directed at obtaining reliable information regarding SLN positivity prior to surgical excision. However, the existing tools, eg. dermoscopy, do not recognize statistically significant predictive criteria for SLN positivity in melanomas.

AIM

To investigate possible association of computer-assisted objectively obtained color, color texture, sharpness and geometry variables with sentinel lymph node positivity.

METHODS

We retrospectively reviewed and analyzed the computerized medical records of all patients, diagnosed with cutaneous melanoma in a tertiary hospital in Germany during a 3-year period. The study included patients with histologically confirmed melanomas with Breslow > 0.75 mm, who underwent lesion excision and SLN biopsy during the study period and for who clinical images, shot with a digital camera and a handheld ruler being aligned beside the lesion, were available.

RESULTS

Ninety-nine patients with equal number of lesions met the inclusion criteria and were included in the analysis. Overall mean (SD) age was 66 (15) years. The study group consisted of 20 patients with tumor-positive SLN biopsy, who were compared to 79 patients with tumor-negative SLN biopsy specimen (control group). The two groups differed significantly in terms of age (61 vs. 68 years) and histological subtype, the SLN+ patients being younger and presenting more often nodular or secondary nodular tumors ($p < 0.05$). The study group patients showed also significantly higher eccentricity (i.e. distance between color and geometrical midpoint), as well as higher

sharpness, i.e. these lesions were more discrete from the surrounding normal skin, $p < 0.05$). Regarding color variables, SLN+ patients demonstrated higher range in all four color intensities (gray, red, green, blue) and significantly higher skewness in three color intensities (gray, red, blue), $p < 0.05$. Color texture variables, i.e., lacunarity were comparable in both groups.

CONCLUSION

SLN+ patients demonstrate significantly higher eccentricity, higher sharpness, as well as higher range in all four color intensities (gray, red, green, blue) and significantly higher skewness in three color intensities (gray, red, blue). Further prospective studies are needed to better understand the effectiveness of clinical image processing in SLN+ melanoma patients.

Key Words: melanoma; skin cancer; image processing; sentinel lymph node

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Core Tip: Computer-aided image analysis can facilitate prediction of SLN positivity. Several color, sharpness and geometry parameters can uni- and multivariately predict positive lymph node occurrence, while color texture can not determine SLN positivity.

INTRODUCTION

Cutaneous melanoma is a highly aggressive tumor that often spreads to local lymph nodes. Sentinel lymph node biopsy (SLNB) is commonly performed to identify nodal metastases because ⁴sentinel lymph node (SLN) status is a strong prognostic factor for survival in melanoma patients, especially in those without evidence of clinically positive lymph nodes^[1]. In some subgroups, e.g., in patients with thick melanomas (i.e.,

Breslow thickness > 4 mm)^[2] and patients with melanomas of the scalp, SLN status is considered the most important prognostic survival factor^[3].

According to the existing guidelines, the decision for SLNB is based on the thickness of the primary tumor. SLNB is indicated for all primary tumors thicker than 1 mm and tumors thicker than 0.75 mm in the presence of ulceration or high mitotic rate (> 1 mm²). SLNB is of crucial importance in the disease's management because positive SLNB should be followed by lymph node dissection for regional disease control and staging purposes. Delays in SLNB may affect the positivity of non-sentinel lymph nodes^[4]. For these reasons, an effort is being directed at obtaining reliable information regarding SLN positivity before surgical excision. Dermoscopy is a non-invasive technique that facilitates early melanoma detection by revealing skin features invisible to the naked eye. However, dermoscopy does not recognize statistically significant predictive criteria for SLN positivity in melanomas because specific melanoma criteria strongly associated with a higher Breslow thickness, such as gray-blue areas or an atypical vascular pattern, do not seem to associate with SLN positivity^[5].

Computer-aided clinical image analysis is also used to improve diagnostic accuracy for skin melanoma. We have shown that geometrical and color parameters objectively extracted by computer-aided clinical image processing may correlate with tumor thickness in patients with cutaneous melanoma^[6]. However, to the best of our knowledge, there is no study investigating the possible association of computer-assisted objectively obtained color, color texture, sharpness, and geometry variables with sentinel lymph node positivity. The aim of this study is to investigate whether such an association exists.

MATERIALS AND METHODS

Patient recruitment

We retrospectively reviewed and analyzed the computerized medical records of all patients diagnosed with cutaneous melanoma in a tertiary hospital in Germany during a three-year period. The study included patients with histologically confirmed

melanomas with Breslow > 0.75 mm, who underwent lesion excision and SLN biopsy during the study period, and for whom clinical images shot with a digital camera and a handheld ruler aligned beside the lesion were available. Patients with melanomas with Breslow < 0.75 mm and in situ melanomas as well as patients without digital images were excluded from the study. Patients referred to our center after primary excision to undergo SLN biopsy were also excluded from the study. The study group consisted of patients with a positive SLN biopsy who were compared to patients with a negative SLN biopsy (control group). Clinical features studied included age, sex, tumor location, and diagnosis date. Histopathologic features included tumor subtype (superficial spreading—de novo and naevus-associated—and nodular, including secondary nodular), Breslow thickness, Clark level, presence of ulceration, nevus preexistence, and SLN status (positive or negative). The study was approved by the institutional review board of the University of Witten-Herdecke.

Image collection, storage system, and image database

All lesions were photographed at admission with the same commercial digital camera at a resolution of 1600×1200 pixels and with a handheld ruler aligned beside the lesion to allow for correct image scaling. All photos were obtained from the same educated nurse to minimize inconsistencies in methodology and were uploaded to a local server. The lesions were then excised under local anesthesia, and the diagnosis was histologically confirmed.

Image processing

All the color images obtained underwent digital processing with an almost fully automated noncommercial software developed by one of the authors (AM) for study purposes. The software applies several kinds of algorithms to allow image segmentation and geometry, color, and color texture analysis (Figure 1). The only manual involvement was the selection of the lesion border with the mouse cursor when the algorithm failed to do so (i.e., in very small lesions). Such cases were independently

analyzed twice by two of the authors (MP and GM) to avoid intra-observer errors. In cases of discrepancies, the mean scores were accepted and further analyzed. The 34 variables studied are classified as follows^[7]: (a) geometrical variables (i.e., area, maximum diameter, perimeter, circularity, eccentricity, and mean radius), (b) color variables (i.e., range, standard deviation, coefficient of variation, and skewness for all four color intensities [gray, red, green, blue]), (c) sharpness variables, and (d) color texture variables (i.e., lacunarity). All variables are thoroughly described in Table 1.

Statistical analysis

Normal distribution was determined using histogram plots, box plots, and the Shapiro-Wilk test. Continuous data are presented in mean-standard deviation form. Categorical variables were compared using the two-tailed Fisher's exact test and continuous ones using the two-tailed Student's t-test. A p-value of less than 0.05 was considered statistically significant. Uni- and multivariate analysis using logistic regression were employed to identify potential independent determinants of a positive SLN result. Data analyses were performed using SPSS 23.

RESULTS

Ninety-nine patients with an equal number of lesions met the inclusion criteria and were included in the analysis. Of these, 52 (52%) were males and the rest (48%) females. ² Histogram plots, box plots, and the Shapiro-Wilk test demonstrated an almost normal distribution appearance for all continuous variables. The overall mean (SD) age was 66 (15) years. ² The youngest patient was 14 years old and the oldest 92. The study group consisted of 20 patients with tumor-positive SLN biopsy, who were compared to 79 patients with tumor-negative SLN biopsy specimens (control group).

The two groups differed significantly in terms of age (61 *vs* 68 years) and histological subtype; the SLN+ patients were younger and presented more often nodular or secondary nodular tumors ($p < 0.05$).

The study group patients also showed significantly higher eccentricity (i.e., the distance between color and geometrical midpoint) and higher sharpness (i.e., these lesions were more discrete from the surrounding normal skin, $p < 0.05$). Regarding color variables, SLN-positive patients demonstrated a higher range in all four color intensities (gray, red, green, blue) and significantly higher skewness in three color intensities (gray, red, blue), $p < 0.05$. Color texture variables (i.e., lacunarity) were similar in both groups. Comparative data are summarized in Table 2.

Multivariate analysis of univariately significant variables ($p < 0.05$) revealed that younger age and higher eccentricity were independently associated with a higher probability of positive lymph node occurrence (for age: aOR = 0.95, 95%CI: 0.91 to 0.99 and for eccentricity: aOR = 1.45, 95%CI: 1.12 to 1.89). Naevus, nodular, and secondary nodular histotypes were also significantly linked with higher odds of positive lymph node presence when compared to SSM histotype (for naevus: aOR = 14.19, 95%CI: 1.15 to 174.76, for nodular: aOR = 10.71, 95%CI: 1.48 to 77.48, and for secondary nodular: aOR = 18.21, 95%CI: 2.19 to 151.22). The proposed multivariate model can predict the presence of positive SLN with an accuracy of 85% and is summarized in Table 3.

DISCUSSION

Computer-aided image analysis is a noninvasive method and, as such, an established tool in the physicians' armamentarium to obtain reliable information regarding malignancy before surgical excision. SLN status is a strong prognostic factor for survival in melanoma patients—the tumor thickness threshold for SLNB being 1 mm—in the absence of risk factors. We herein investigated the possible association of computer-assisted objectively obtained color, texture, and geometric variables with sentinel lymph node positivity.

SLN-positive patients have a higher range in all four color intensities (gray, red, green, blue) and significantly higher skewness in three color intensities (gray, red, blue). Blue and black pigmentation is associated with the presence of nodular melanoma^[8], which, in our study, accounted for 50% of the SLN+ tumors. Malignant epidermal structures, (e.g., atypical pigment network, radial streaks, and pseudopods) are rarely seen in SLN+ melanomas, while they are observed in one-fourth of SLN negative lesions^[5].

Despite the significant differences in all color intensities, we found that lacunarity—a measure of the variation of the color intensity—although a proven promising parameter in the automated differentiation of melanoma from non-melanoma^[9], cannot predict SLN status within melanoma patients. We also found the lesions of SLN+ patients have significantly higher eccentricity, which is an index of uneven lesion coloration. Eccentricity represents a special case of asymmetry and, as shown before, eccentric lesions may be thicker^[6]. Dermoscopically, only the presence of ulceration and blotch correlate with positive SLNB^[10].

Regarding histological type, González-Álvarez *et al* found nodular melanomas to be the most associated with SLN positivity, reporting an OR of 3.98^[10]. This is consistent with our findings, where half of the SLN+ tumors were nodular and the OR was 14.4. Moreover, we found that secondary nodular tumors are much more often associated with positive SLN, the OR exceeding 25. This may reflect more aggressive tumor growth because angiolymphatic invasion is observed in the majority of nodular melanomas with SLN positivity^[5]. According to our findings, a multivariate model consisting of age, histological type, and eccentricity can predict the presence of positive SLN with an accuracy of up to 85%.

A recent study describes a deep learning-based digital biomarker to predict SLN+ from digitized H&E slides of primary melanoma tumors. Artificial neural networks predicted SLN status with an accuracy of 55–62%^[11]. This relatively low accuracy is attributed to morphological changes of the tumor cells or tumor architecture. Moreover, the histopathological workup may have caused tumor cells to be missed in the lymph nodes. Neural networks failed to detect features other than thickness and age that

predict SLN positivity. We found that higher values of eccentricity, sharpness, blue, gray, green range, red skewness, and red mean could also predict positive lymph node occurrence.

Our study is limited regarding its retrospective nature and small sample size. First, it is a single-center study of German individuals, and therefore, the results cannot be easily generalized. Second, only melanoma patients with available clinical images made before the diagnosis was established were included. Therefore, there is a high risk of bias due to no consecutive cases being included. Selection bias may have led to suspect cases being more frequently given the possibility to be photographed. Moreover, we excluded all patients with melanomas with Breslow thickness < 0.75 mm. However, the specimens were analyzed by different pathologists during the study period, so the interpretation bias of tumors' thickness may have led to eligible cases being excluded.

CONCLUSION

In conclusion, computer-aided image analysis can facilitate the prediction of SLN positivity. SLN+ patients demonstrate significantly higher eccentricity, higher sharpness, and higher range in all four color intensities (gray, red, green, blue) as well as significantly higher skewness in three color intensities (gray, red, blue). Further prospective studies are needed to better understand the effectiveness of clinical image processing in SLN+ melanoma patients.

ARTICLE HIGHLIGHTS

Research background

Computer-aided clinical image analysis is also used to improve diagnostic accuracy for skin melanoma.

Research motivation

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To the best of our knowledge, there is no study investigating the possible association of computer-assisted objectively obtained color, color texture, sharpness, and geometry variables with sentinel lymph node positivity.

Research objectives

To investigate possible association of computer-assisted objectively obtained color, color texture, sharpness and geometry variables with sentinel lymph node positivity.

Research methods

The study included patients with histologically confirmed melanomas with Breslow > 0.75 mm, who underwent lesion excision and SLN biopsy during the 3-year study period and for who clinical images, shot with a digital camera and a handheld ruler being aligned beside the lesion, were available. All the color images obtained underwent digital processing with an almost fully automated noncommercial software developed by one of the authors for study purposes.

Research results

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Ninety-nine patients with equal number of lesions met the inclusion criteria and were included in the analysis. The study group consisted of 20 patients with tumor-positive SLN biopsy, who were compared to 79 patients with tumor-negative SLN biopsy specimen (control group). The study group patients showed significantly higher eccentricity (i.e. distance between color and geometrical midpoint), as well as higher sharpness, i.e. these lesions were more discrete from the surrounding normal skin, $p < 0.05$). Regarding color variables, SLN+ patients demonstrated higher range in all four color intensities (gray, red, green, blue) and significantly higher skewness in three color intensities (gray, red, blue), $p < 0.05$. Color texture variables, i.e, lacunarity were comparable in both groups.

Research conclusions

Computer-aided image analysis can facilitate the prediction of SLN positivity. SLN+ patients demonstrate significantly higher eccentricity, higher sharpness, and higher range in all four color intensities (gray, red, green, blue) as well as significantly higher skewness in three color intensities (gray, red, blue).

Research perspectives

Further prospective studies are needed to better understand the effectiveness of clinical image processing in SLN+ melanoma patients.

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