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OPHTHALMIC PLASTIC AND RECONSTRUCTIVE SURGERY, PHILADELPHIA, v. 28, n. 4, pp. 282-285, JUL-AUG, 2012
<http://www.producao.usp.br/handle/BDPI/42328>

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Is 2-mm Punch Biopsy Useful in the Diagnosis of Malignant Eyelid Tumors?

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Purpose: Two-millimeter punch biopsy is a swift and practical diagnostic tool in the outpatient setting. However, few studies have evaluated the efficacy of the method for diagnosis of malignant eyelid tumors.

Methods: This was an observational study of patients with suspicion of malignant eyelid tumor attending the Ocular Plastic Surgery Center at Hospital das Clínicas, University of São Paulo School of Medicine. Following standard procedures, preoperative biopsies were taken with a 2-mm trephine and surgical excision was performed with safety margins, followed by reconstruction. Anatomopathologic analysis of the surgical specimen was used as gold standard to evaluate the accuracy of diagnosis by punch biopsy.

Results: The study included 50 periocular tumors with suspicion of malignancy. The indicators of efficacy in the identification of malignancy by 2-mm punch biopsy were: sensitivity 88%, specificity 100%, positive predictive value 100%, and negative predictive value 64%. Accuracy was 90% for malignancy and 80% for histologic type. The κ index of agreement between the diagnostic methods was 0.722 ($p < 0.001$).

Conclusion: A positive result with 2-mm punch biopsy is a safe indication for surgical excision of the tumor, whereas a negative result does not necessarily imply benignity. In cases of high clinical suspicion, a second biopsy should be taken from a different part of the tumor to rule out malignancy.

(*Ophthalm Plast Reconstr Surg* 2012;28:282–285)

Approximately 5% to 10% of all skin neoplasms affect the eyelid. In fact, periocular malignancy is the most common type of neoplasm observed at our service.¹ Due to their small size, periocular tumors can be hard to diagnose and surgery is often postponed when clinical findings are ambiguous. Despite considerable accuracy in the diagnosis of malignancy, clinical evaluation of patients with periocular tumors frequently yield false-positive and false-negative results, and on the average clinical and histologic findings are poorly correlated.^{2–5}

Several factors have been associated with recurrence of periocular tumors after treatment, such as size, location, and medical conditions related to histologic type.⁶ Aggressive tumors require larger surgical margins and pose a greater risk of metastasis.

Punch biopsy is a swift and simple diagnostic technique requiring very little equipment or surgical skill. A 2-mm trephine will collect a tissue sample large enough for analysis and no suture is necessary. The level of agreement between punch biopsy, conventional incisional biopsy, and histopathologic analysis of the surgical specimen is high.^{7–9}

Punch biopsy can be useful in preoperative assessments of skin disorders.⁷ However, the few published studies on punch biopsy in the periocular region—rarely cited by ophthalmologists—lack a complete evaluation of efficacy, especially with regard to histologic type.^{8,9}

OBJECTIVE

The aim of this study was to evaluate the ability of 2-mm punch biopsy to diagnose malignancy and define the histologic type of eyelid tumors.

MATERIALS AND METHODS

This was an observational study of patients with eyelid tumors suspected for malignancy attending the Ocular Plastic Surgery Center of the Department of Ophthalmology, Hospital das Clínicas, University of São Paulo School of Medicine (HC-FMUSP), between November 2007 and December 2010.

Tumors displaying clinical signs of malignancy on biomicroscopy (changes in texture, color, and size associated with ulceration, raised and/or ulcerated surface, irregular outline, telangiectasias and/or loss of eyelashes) were included in the study. The study was previously approved by the research ethics committee of the institution (HC-FMUSP #1143/07) and was registered with ClinicalTrials.gov under #NCT00865813. All patients gave their written informed consent.

Following standard procedures, preoperative biopsies were taken from the most typical part of the tumor—usually a pearly patch or the border. The procedure which was done at the HC-FMUSP outpatient surgery service, included the following steps:

1. Instillation of anesthetic eyedrops.
2. Asepsis and antisepsis.
3. Placement of sterile drapes.
4. Infiltration of region with anesthetic solution containing adrenaline at 1:200,000.
5. Insertion of a 2-mm stainless steel trephine (Richter) into the tumor tissue by applying light pressure and rotation (Fig. 1A).
6. Exposure of the biopsied material using an insulin needle or

Accepted for publication April 10, 2012.

The study was conducted at the Ocular Plastic Surgery Center, Department of Ophthalmology, Hospital das Clínicas, University of São Paulo School of Medicine, São Paulo, Brazil.

The authors have no financial or conflict of interest to disclose.

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DOI: 10.1097/IOP.0b013e31825a65b4

conjunctiva forceps, followed by severing of the biopsy specimen with a scalpel size 11 (Fig. 1B, C).

7. Placement of dressing with ophthalmological ointment containing 0.5% gentamicin (Allergan).
8. Biopsy material was secured in a labeled vial of 10% formalin (Fig. 1D).

Within 15 to 30 days, patients underwent surgical tumor excision with adequate safety margins, followed by reconstruction of the tumor site.

The histopathologic examination was performed at the Department of Pathology by pathologists masked to the biopsy results. Discordant slides were reviewed by a nonmasked pathologist.

Histopathologic analysis of the surgical specimen was used as gold standard to evaluate the accuracy of diagnosis by punch biopsy. The tumor type was determined histologically based on growth patterns in hematoxylin and eosin stains.

The performance standards of 2-mm punch biopsy were studied using histopathologic diagnosis of the totally excised tumor as the gold standard.

RESULTS

Fifty patients aged 29 to 90 years (average: 63) were evaluated, of whom 19 (38%) were men and 31 (62%) were women. Based on Fitzpatrick's classification¹⁰ of skin type, 4 were Type I (8%), 14 Type II (28%), 20 Type III (40%), 10 Type IV (20%), and 2 were Type V (4%). The tumor was located either on the lower eyelid (n = 38; 76%), the inner corner (n = 8; 16%), or the upper eyelid (n = 4; 8%) (Table 1).

Tumors were malignant in 41 cases (82%) and benign in 9 (18%). Basal cell carcinoma was predominant (n = 29; 71%) among malignant tumors, followed by squamous cell carcinoma (n = 10; 24%), and melanoma (n = 2; 5%). Melanocytic nevus was predominant (n = 5; 56%) among the benign tumors, followed by granuloma (n = 2; 22%), molluscum contagiosum (n = 1; 11%), and squamous cell papilloma (n = 1; 11%).

Evaluation of Agreement for Diagnosis of Malignancy. Five cases diagnosed as benign in the biopsy were found to be malignant upon excision (false-negative) (Table 2).

Table 1. Sample characteristics

Gender	
Men	19 (38%)
Women	31 (62%)
Average age	63 (29–90)
Fitzpatrick Classification	
Type I	4 (8%)
Type II	14 (28%)
Type III	20 (40%)
Type IV	10 (20%)
Type V	2 (4%)
Tumor site	
Lower eyelid	38 (76%)
Inner corner	8 (16%)
Upper eyelid	4 (8%)
Tumors	50
Benign	9 (18%)
Nevus	5
Granuloma	2
Molluscum	1
Papilloma	1
Malignant	41 (82%)
BCC	29
SCC	10
Melanoma	2

BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

Table 2. Correlation between 2-mm punch biopsy and anatomopathologic findings (malignancy diagnosis)

Excised specimen		Malignant	Benign	Total
Biopsy	Malignant	36	0	36
	Benign	5	9	14
	Total	41	9	50

Table 3. Accuracy with regard to histologic type

Biopsy	Excised specimen
Actinic elastosis	BCC
Granuloma	BCC
Actinic keratosis	Actinic keratosis + SCC
Actinic keratosis	SCC
Actinic keratosis	SCC
False-negative	5
Actinic keratosis	Granuloma
True-negative	1
Actinic keratosis + SCC	BCC
Tumor of skin appendages	BCC
BCC	SCC
SCC	BCC
True-positive	4
Cases of disagreement	10
Accuracy	80%

BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

Performance standards:

- Prevalence (pretest probability): 82%
- Sensitivity: 88%.
- Specificity: 100%.
- Positive predictive value: 100%.
- Negative predictive value: 64%.
- Accuracy: 90% for presence of malignancy.
- κ index: 0.722 ($p < 0.001$) (good level of agreement).

Evaluation of Agreement for Histologic Type. The 2 diagnostic methods disagreed with regard to histologic type in 10 of 50 cases (accuracy: 80%). Five cases diagnosed as benign histologic type in the biopsy were found to be malignant upon excision (false-negative results). Four of the true-positive cases disagreed with regard to histologic type, despite agreement regarding malignancy. Among the true-negative cases, the identification of histologic type diverged for a single tumor diagnosed by both methods as benign (Table 3).

DISCUSSION

Todd et al.⁷ found a high level of agreement (94%) between 2-mm punch biopsy and elliptical incisional biopsy in different skin tumors. This finding and the simplicity of the procedure (no suture is required) has contributed to disseminate 2-mm punch biopsy in dermatological practice.

In a retrospective study on periocular tumors, Rice et al.⁸ evaluated the agreement between 2-mm punch biopsy, elliptical incisional biopsy, and histopathologic analysis of the surgical specimen. Agreement was 85% for punch biopsy and 95% for incisional biopsy. However, no other performance standards were reported.

The importance of 3-mm punch biopsy in the management of periocular basal cell carcinoma was evaluated retrospectively by Chatterjee et al.⁹ Agreement was reasonable between clinical findings and punch biopsy (sensitivity 87.5%, specificity 75%, positive predictive value 87.5%, and negative

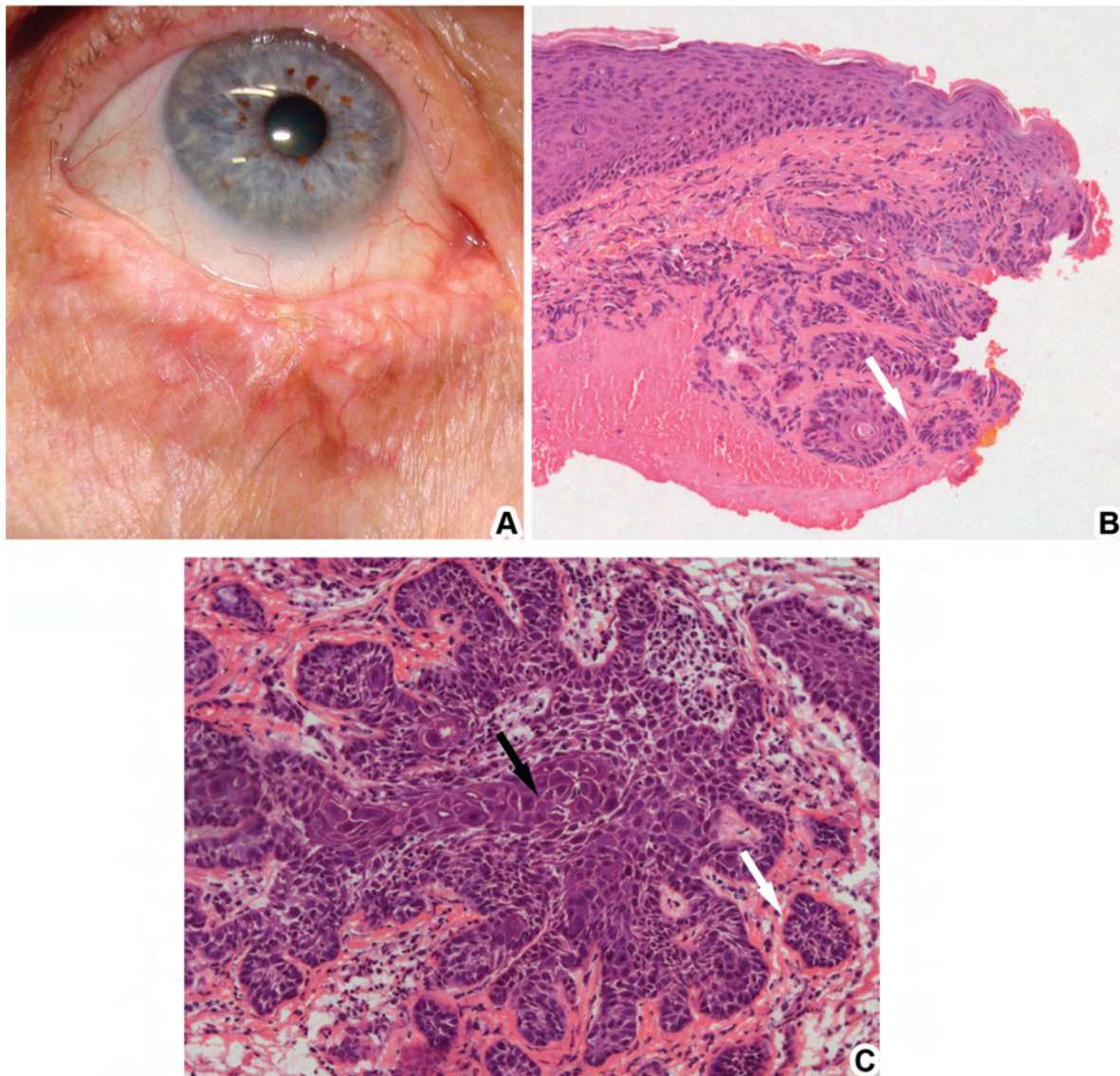


FIG. 1. **A**, Patient with ulcerated lesion; **B**, punch biopsy: small lobules of atypical basaloid cells showing invasion of the superficial and middle dermis (*white arrow*). Hematoxylin-eosin (x200), overall view; **C**, surgical specimen. At the periphery (*white arrow*) areas with keratinization and a basaloid aspect; however, in the center (*black arrow*), the squamous nature of the tumor is apparent. Hematoxylin-eosin (X200).

predictive value 75%). However, due to lack of specimens for analysis (only 13 of 24 patients underwent surgical excision), the 2 methods could not be compared with the gold standard.

Both 3-mm and 4-mm punch biopsy and elliptical incisional biopsy require 1 or 2 stitches to repair the site of sample collection. In contrast, 2-mm punch biopsy makes a suture unnecessary, saving time, surgical supplies, and resources.⁸

The main factor determining the usefulness of a diagnostic method is accuracy. In addition to a high level of accuracy (90%), 2-mm punch biopsy displayed high levels of sensitivity (88%), specificity (100%), positive predictive value (100%), and negative predictive value (64%) for the diagnosis of malignant eyelid tumor.

Since clinical examinations can yield ambiguous results, confirmation of malignancy by 2-mm punch biopsy is a useful aid in the choice of surgical approach. Patients with early malignant eyelid tumors are not uncommonly misdiagnosed with trichiasis, blepharitis, meibomitis, and other inflammatory conditions. A

100% specificity means no false-positive results, thus no unnecessary surgery. A simple biopsy can change the course of the disease by serving as a guide in the treatment of a malignant tumor.

The high level of reliability ($\kappa = 0.722$) in the evaluation of agreement between 2-mm punch biopsy and histopathologic analysis rules out chance as the explanation of the results. Accuracy was greater for the presence of malignancy (90%) than for histologic type (80%)

Areas with precursor lesions such as actinic elastosis, actinic keratosis, and inflammatory infiltrate can lead to false-negative results for malignancy (Table 3). This is reflected by the fact that negative predictive value was lower (64%) than the other indices. Thus—confirming observations made by other authors⁸ in cases of high clinical suspicion and negative findings for malignancy, a second biopsy should be taken from a different part of the tumor.

The main limitation of the technique is sample size, which can compromise the identification of the tumor histologic type as showed in Figure 2.

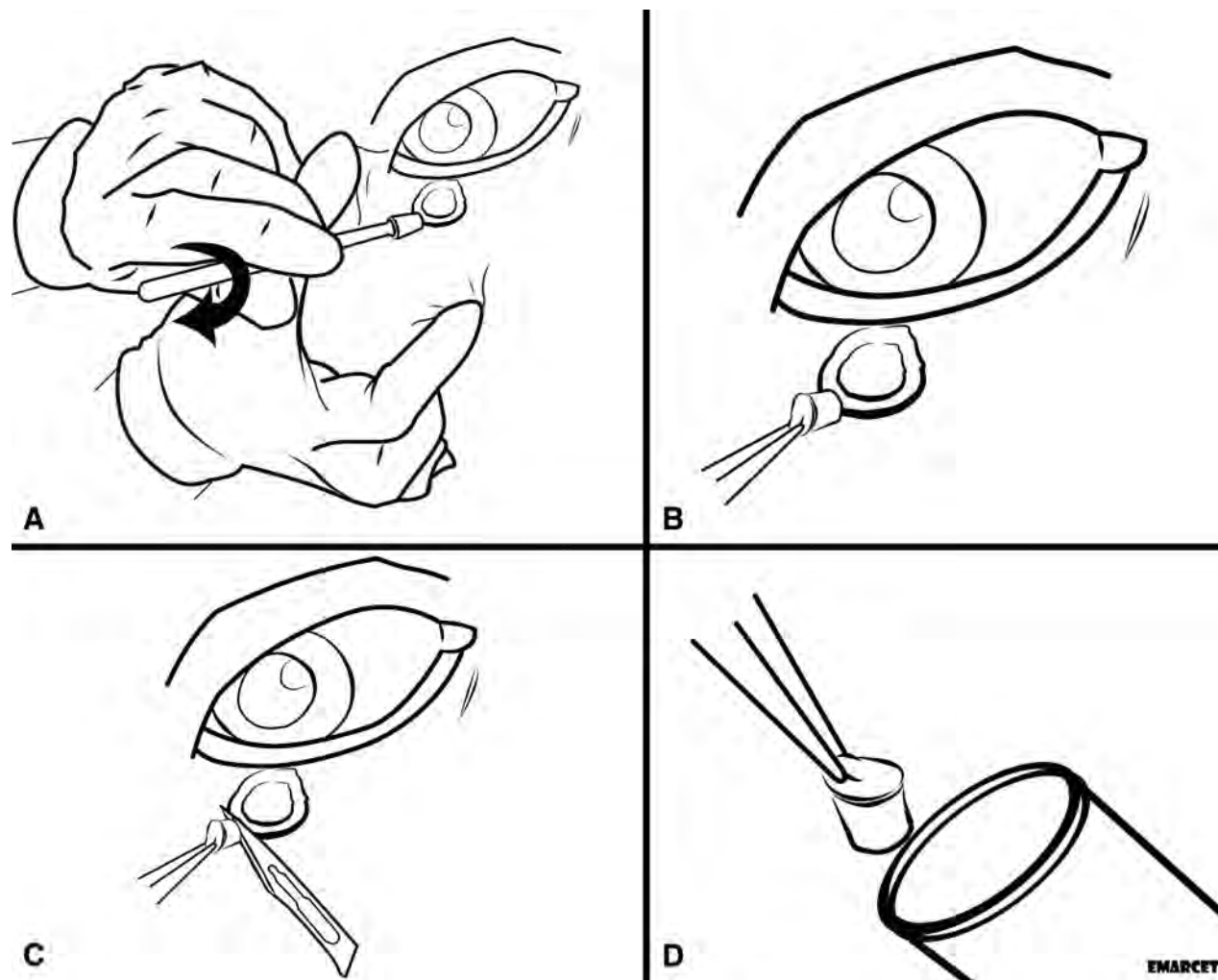


FIG. 2. **A**, Insertion of a 2-mm stainless steel trephine into the tumor tissue by applying light pressure and rotation. **B**, Exposure of the biopsied material using a conjunctiva forceps. **C**, Followed by severing of the biopsy specimen with a scalpel size 11. **D**, Biopsy material was secured in a labeled vial of 10 formalin.

The present study shows that a positive result with 2-mm punch biopsy is a safe indication for surgical excision of the tumor (Table 3), whereas a negative result does not necessarily imply benignity. In this study of 50 patients, the false-negative rate was 12% (1 – sensitivity), suggesting about 1 in 10 clinically suspicious malignancies of the eyelid may be missed with a 2-mm punch biopsy. Therefore, in cases of high clinical suspicion, if the clinical impression does not fit the histopathologic diagnosis, perform biopsy again from a different part of the tumor to rule out malignancy.

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