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Diagnosis of aggressive subtypes of eyelid basal cell carcinoma by 2-mm punch biopsy: prospective and comparative study

Diagnóstico dos subtipos agressivos de carcinoma basocelular palpebral pela biópsia por trépano de 2mm: estudo prospectivo e comparativo

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ABSTRACT

Objective*: to compare the accuracy of preoperative 2-mm punch biopsy at one site and at two sites in the diagnosis of aggressive subtypes of eyelid basal cell carcinoma (BCC).* **Methods***: we randomly assigned patients to Group 1 (biopsy at one site) and Group 2 (biopsy at two sites). We compared the biopsy results to the gold standard (pathology of the surgical specimen). We calculated the sensitivity, specificity, positive predictive value, negative predictive value, accuracy and Kappa coefficient to determine the level of agreement in both groups.* **Results***: we analyzed 105 lesions (Group 1: n = 44; Group 2: n = 61). The agreement was 54.5% in Group 1 and 73.8% in Group 2 (p = 0.041). There was no significant difference between the groups regarding the distribution of quantitative and qualitative variables (gender, age, disease duration, tumor larger diameter, area and commitment of margins). Biopsy at two sites was two times more likely to agree with the gold standard than the biopsy of a single site.* **Conclusions***: the accuracy and the performance indicators were better for 2-mm punch biopsy in two sites than in one site for the diagnosis of aggressive subtypes of eyelid BCC.*

Keywords: *Biopsy. Eyelid Neoplasms. Efficacy.*

INTRODUCTION

Several benign and malignant tumors can develop in the periocular skin from the epidermis, dermis and attachments. The appearance and behavior of the eyelids may be different from the rest of the body, in part by the characteristics of the skin eyelid and its specialized attachments. The first concern is to appropriately rule out malignancy[1].

About 5 to 10% of all skin cancers occur on the eyelid, which is the main site of neoplasms in the ophthalmological clinical practice. Another important aspect is that the normal peritumoral tissues should be minimally violated to preserve functionality and prevent deformity[2].

Basal Cell Carcinoma (BCC) is the most common type of skin cancer, accounting for 75% of malignant epithelial tumors and for 90% of cases affecting the eyelids[3-14]. Some tumor subtypes behave more aggressively due to a greater tendency to incomplete excision and recurrence, and greater chance of local and distance spread[8-15]. Thus, the diagnosis of aggressiveness becomes important to ensure sufficiently large surgical margins.

Despite having high accuracy for the diagnosis of malignancy, clinical examination has considerable false negative and false positive rates, also showing a poor correlation between the clinical and histologic type of lesion[1,16,17]. In the literature, the accuracy of eyelid malignancy clinical diagnosis lies between 65% and 96%[18].

The incisional punch biopsy is a quick and simple diagnostic procedure that requires minimal equipment and surgical skill. The use of the 2-mm diameter punch makes suture unnecessary, besides providing an appropriate-size tissue and high level of agreement with the traditional incisional biopsy and the final histopathologic examination of the specimen[12, 13, 19].

The punch incisional biopsy is extremely useful in the preoperative evaluation of dermatologic disorders[19]. It is not widely spread in ophthalmology and the

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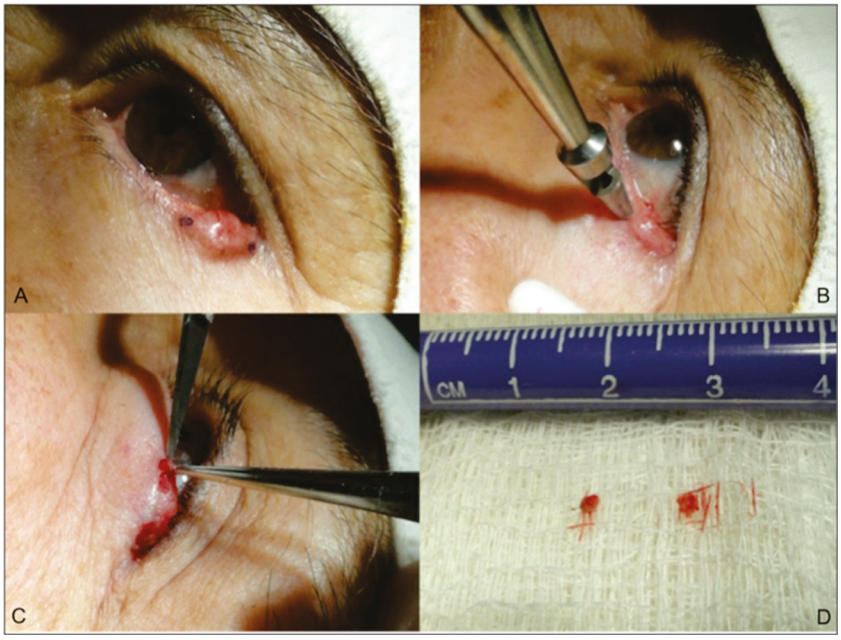

Figure 1. *Steps of the 2-mm punch biopsy at two sites (Group 2). (A) tumoral lesion on the lower eyelid, with markings on the sites to be punched; (B) Punching of the lesion with a stainless steel 2-mm punch; (C) fragment withdrawal with clamp and number 11 scalpel blade; (D) Specimens.*

few studies involving the eyelid area did not fully evaluated its effectiveness, mainly for assessment of the lesion histologic subtype[12,13].

We expect better accuracy when the diagnosis relies on two biopsy sites. Thus, it would facilitate the planning of surgical margins and patient follow-up, especially in medical services where the intraoperative appraisal of surgical margin is not available. The aim of this study was to compare the accuracy of the 2-mm punch preoperative biopsy at one site with the same biopsy in two sites for the diagnosis of aggressive subtypes of eyelid BCC.

METHODS

We conducted a prospective, randomized, masked study of consecutive patients with suspected malignant eyelid lesions from November 2012 to December 2014, examined in the Oculoplastic sector of the Ophthalmology Clinics of the Clinics Hospital, Faculty of Medicine, University of São Paulo (HCFMUSP). The research project was approved by the Ethics Committee for Projects and Research (CAPPesq) of the Faculty of Medicine of the University de São Paulo (research protocol number 1143/07). All participants signed an informed consent.

We included 105 cases with clinical suspicion of malignancy at biomicroscopy (changes in texture, color, pigmentation and size associated with ulceration, raised surface, irregular borders, telangiectasias or loss of cilia) that were later confirmed as BCC by the gold standard (pathological examination of the surgical specimen excised with a safety margin and frozen section analysis). We excluded cases of prior knowledge of diagnosis, recurrent tumors or lesions with dimensions below 4 mm wide at their largest diameter.

All lesions were previously documented with digital camera (Sony DSC-W125, Sony Corporation, Tokyo, Japan) fixed on a tripod, in optimal quality, and subsequently measured with the aid of software Image J 1.44 (National Institute of Mental Health, Bethesda, Maryland , USA) to obtain the larger diameter and area.

We randomly divided patients into two groups (head/tail): Group 1, submitted to 2-mm punch biopsy in a single site of the lesion, in a standardized form, on the tumor most typical site; Group 2, submitted to 2-mm punch biopsy at two sites, diametrically oppose to each other in the lesion larger diameter.

Procedure 1: the same author (LAR) performed all punch biopsies in the Outpatient Surgery Center of HC-FMUSP, following the steps shown in Figure 1.

Procedure 2: within 15 to 60 days, we held the excisional surgery with a safety margin and frozen section analysis. The reconstruction of the defect was performed during the same operation, with the most appropriate technique for each case.

The same pathologist (PPL) performed the pathologic evaluation of all specimens. The histological subtype lesions were identified by their growth pattern observed on hematoxylin-eosin on microscope at 200x, 400x and 1000x (immersion) magnifications, when need-

ed. We classified tumors according to WHO[4]. To mixed tumors, we used the predominant and accessory patterns. The predominant histological type corresponds to the pattern present in more than 50% of the lesion. Histological accessories types are the other patterns, found in smaller proportions[20].

The BCC subtypes considered aggressive are micronodular, infiltrative, sclerodermiform, basosquamous and metatypical, including mixed tumors with aggressive component. The non-aggressive subtypes are the nodular and superficial BCC[4,5,7,8,15,21].

To determine the effectiveness of the 2-mm punch in the diagnosis of BCC subtypes, we evaluated the degree of agreement between the 2-mm punch biopsies and the gold standard. We compared the results between patients in both groups and calculated the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. We performed the Kappa agreement analysis. For the quantitative variables (age, duration, larger diameter, tumor area) we used the Mann-Whitney test, and for the qualitative ones (gender, location, involvement or not of eyelid margin), the chi-square or Fisher's exact tests due to data's non-adherence to the normal distribution and/or presence of variances heterogeneity.

We analyzed the concordant results by logistic regression to identify the associated factors. We set the significance level at 5%. We analyzed the data using SPSS (Statistical Package for Social Sciences) version 18.

RESULTS

We included 105 BCC cases, 44 in Group 1 and 61 in Group 2. Table 1 shows the characteristics of the two groups and levels of statistical significance (p-value).

For all variables, quantitative and qualitative, the distribution between groups was similar (p-value greater than 0.05), except for the time of disease progression, with p-value of 0.049.

Table 2 compares the results for both punch biopsy and the gold standard in the diagnosis of a BCC aggressive subtype in both groups. The agreement in Group 1 was 54.50%, and in Group 2, 73.80%, with no statistical difference (p-value 0.041) (Table 3). Table 4 shows the performance indicators.

Table 1. *Characteristics of patients and tumors in Group 1 (biopsy in one site) and Group 2 (biopsy in two places).*

Variable	Group 1	Group 2	p-value
Age (Years)*	67.95	67.05	0.610**
Gender			
Female	21 (47.7%)	33 (54.1%)	0.519***
Male	23 (52.3%)	28 (45.9%)	
Evolution time (Years)*	2.38	1.84	0.049**
Largest diameter (mm)*	11.30	11.42	0.721**
Area (mm^2)*	74.38	77.20	0.969**
Location			
Lower eyelid	29 (65.9%)	50 (82.0%)	0.094†
Upper Eyelid	1 (2.3%)	3 (4.9%)	
Medial Corner	10 (22.7%)	7 (11.%)	
Lateral Corner	4 (9.1%)	1 (1.6%)	
Involvement of the margin			
Yes	27 (61.4%)	44 (72.1%)	0.245***
No	17 (38.6%)	17 (27.9%)	

** Average; ** Mann-Whitney Test; *** Chi-square test; † Fisher exact test*

Table 2. *Description of the punch biopsy and the gold standard results for the diagnosis of aggressive subtypes of BCC in both groups.*

	Punch biopsy		Gold standard	
	n	Frequency (%)	n	Frequency (%)
Group 1				
Aggressive				
Micronodular BCC	3	6.82	7	15.91
Sclerodermiform BCC	8	18.18	8	40.91
Metatypical BCC	2	4.55	0	0
Well-differentiated SCC	1	2.27	0	0
Non-aggressive				
Nodular BCC	25	56.82	16	38.64
Superficial BCC	1	2.27	3	4.55
Actinic Keratosis/inflammatory process	4	11.36	0	0
TOTAL	44	100	44	100
Group 2				
Aggressive				
Micronodular BCC	2	3.28	5	8.20
Sclerodermiform BCC	15	24.59	18	29.51
Basosquamous BCC	3	4.92	1	1.64
Metatypical BCC	5	8.20	13	21.31
Non-aggressive				
Nodular BCC	27	44.26	21	34.43
Superficial BCC	0	0	3	4.92
Actinic Keratosis/inflammatory process	9	14.75	0	0
TOTAL	61	100	61	100

BCC = Basal Cell Carcinoma; SCC = Squamous Cell Carcinoma.

DISCUSSION

Eyelid tumors are the most common in the ophthalmologic practice and the BCC is at least 90% of all case[17]. It occurs more often in men after the age of 40, in people of light skin and eyes, red hair, with history of prolonged exposure to sunlight and sunburn during childhood and people with Fitzpatrick skin phototypes I, II and III. Family history and immunosuppressive therapy are also risk factors[3, 6-8, 22, 23].

The classic clinical aspect of BCC is a rounded papule with pinkish or pearlescent color, elevated areas (usually on the periphery of the lesion), central depression and telangiectasia (Figure 2). The frequency of location in the eyelid follows, in descending order: lower eyelid, medial corner, upper eyelid and lateral corner.

BCC has different histological subtypes, and their different clinical behaviors are the basis for the World Health Organization (WHO) classification system[4]. There are four main groups: nodular, micronodular, superficial and infiltrative. The nodular group is divided into solid and adenoid cystic. There are less common subtypes, such as sclerodermiform (or morpheaform - considered by some authors as a variant of infiltrative), basosquamous carcinoma (characterized by squamous atypia associated with greater tendency to recurrence and metastasis), and the metatypical carcinoma (shows cells in a stage between the BCC and a squamous cell carcinoma – SCC)[5, 6, 9].

Table 3. *Agreement between the punch biopsy and the gold standard in the diagnosis of aggressive subtypes of BCC in both eyes.*

Agreement	Total	Group 1	Group 2	p-value*
Sim	69 (65.70%)	24 (54.50%)	45 (73.80%)	0.041
Não	36 (34.30%)	20 (45.50%)	16 (26.20%)	

** Chi-square test*

The most common subtype is the nodular (66.5%) (Figure 2) followed by the superficial, infiltrative and micronodular. Very commonly, more than one subtype are found in the same lesion, and the most common association is the nodular and micronodular subtypes[3,6,8,21].

The nodular BCC has a lower tendency of deep local infiltration and recurrence than the others[21]. The infiltrative and micronodular subtypes are considered of high risk due to the most aggressive behavior and high tendency to incomplete excision and thus recurrence, especially on the face, where surgical margins are conservative. The superficial subtype occurs in younger people[19, 20, 24, 25]. The non-aggressive subtypes (superficial and nodular) are surrounded by an area of basal membrane containing collagen types IV and V with laminin, which does not happen with the aggressive ones (micronodular, infiltrative, sclerodermiform and metatypical)[8,15].

The treatment of eyelid tumors involves a number of factors that may influence their recurrence, such as size, location, associated medical conditions and histological type. Tumors that are more aggressive require major surgical margins and, in some cases, pose a risk of metastasis[10].

The most effective treatment of BCC is surgical excision with margin analysis by frozen section or by Mohs micrographic surgery (MMS). The nodular and superficial subtypes are most often completely removed (93.6 to 96.4%), while the micronodular, infiltrative and sclerodermiform have higher rates of margins positive for tumor cells (18.6 to 33.3%). Therefore, one should plan wider surgical margins for such subtypes. The recurrence in these cases can reach 39%, while for completely excised tumors, it is about 1%[5,21].

It is important to get clear margins and at the same time preserve as much healthy tissue as possible for good aesthetic and functional results, maintaining the protection and lubrication of the eyeball. Aggressive subtypes require wider surgical margins and more stringent postoperative monitoring, while less aggressive lesions can be excised with lower margins or treated medically[12,13,19,23,26]. Some authors recommend a surgical margin of 2 to 4 mm for primary tumors, and 5 to 10 mm for sclerodermiform and recurrent cases[24].

Several methods can be used for the diagnosis, among them the biopsy, which consists of a simple and widely applicable procedure, which provides, through histopathological analysis, relevant information to establish a diagnosis of the lesion. Techniques include the traditional elliptical one, the shaving biopsy, the punch biopsy and the excisional one[27].

The punch biopsy was first used by Edward Keyes in 1879. The punch is a hollow circular instrument, made of disposable material or stainless steel, with bev-

Table 4. *Performance Indicators of the punch biopsy in the diagnosis of aggressive subtypes of BCC in both groups.*

Indicators	Group 1	Group 2
Sensitivity	44% (26.67% - 62.93%)	65.79% (49.89% - 78.79%)
Specificity	68.42% (46.01% - 84.64%)	86.96% (67.87% - 95.46%)
PPV	64.71% (41.30% - 82.69%)	89.29% (72.80% - 96.29%)
NPV	48.15% (30.74% - 66.01%)	60.61% (43.68% - 75.32%)
Accuracy	54.55% (40.07% - 68.29%)	73.77% (61.56% - 83.16%)
Kappa	0.118 (0.158 - 0.385)	0.486 (0.248 - 0.723)

PPV = positive predictive value; NPV = negative predictive value.

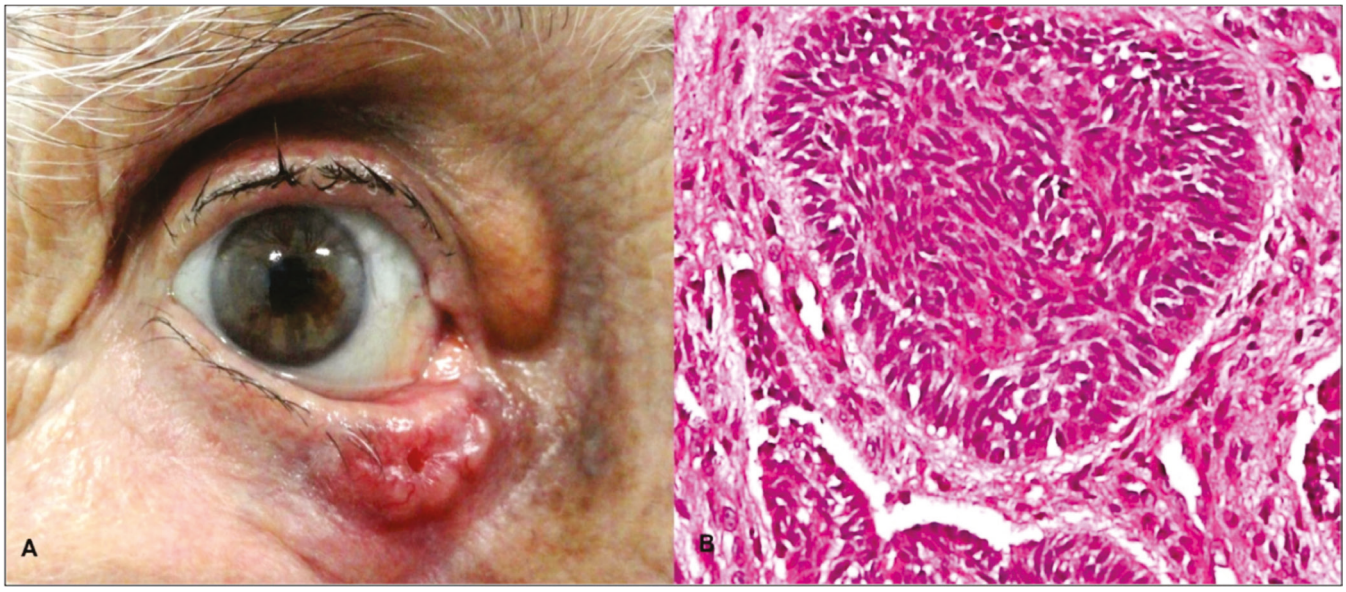

Figure 2. *(A) Clinical aspect of nodular BCC; (B) Nodular BCC histology in hematoxylin and eosin staining, showing a nest of basaloid cells (40x magnification).*

eled and tapered end, which can be of various diameters (from 2 to 10 mm), with which one can obtain a lesion fragment containing all of the skin layers[27].

Some studies compared the result between the 2-mm punch biopsy and the ellipse or shaving and found no statistical difference[11-13,15,19,23,26]. There is reported accuracy of 80 to 85% for BCC subtypes[11,12,26] and there is 94% agreement[19] between the 2-mm punch biopsy and the ellipse one. Carneiro et al demonstrated an accuracy of 90% for malignancy with one biopsy site done by 2-mm punch in eyelid lesions[23]. Of these reports, only three studied eyelid tumors[12,13,23].

In our study, we found greater accuracy in the BCC's aggressiveness diagnosis with 2-mm punch biopsy in two places. The agreement for the biopsy performed on one site was 54.5%, while for two sites it was 73.80%, with no statistical difference (p-value 0.041). The false negative rate was higher in Group 1 (56% versus 34.21%). Furthermore, in Group 1 the diagnosis of the most commonly found BCC aggressive subtype, the sclerodermiform, was less frequent than in Group 2. In addition, the performance indicators were better for punch biopsy in two sites.

Biopsy should allow the surgeon better surgical planning. Thus, the 2-mm punch biopsy in two sites proved to be more effective than in a single site in the diagnosis of infective lesions of BCC, allowing for better surgical preparation and a more adequate security margin, to improve cosmetic and functional results for the reconstruction after tumor excision. These are important factors in services where intraoperative frozen section examination or MMS are not available.

The punch biopsy has advantages that facilitate its performance and provides reliability to the result. In the present study, biopsies were performed with a 2-mm punch; thus, the punched area is small and does not require suturing. This facilitates its realization, in short time, with good healing, low incidence of infection and bleeding, usually without a significant defect, and increases patient compliance in being submitted to it. It also saves time, surgical equipment and resources, and can be performed in an outpatient setting and practice, all important factors in medical services where there is difficulty in the surgical schedule and shortage of material[12,19,23].

The main limitation of the 2-mm punch biopsy technique is actually the size of the tissue sample, which can compromise the identification of histological type or subtype. The punch biopsy in two places sought to meet the representativeness of the lesion to include other histological patterns. There is the possibility of tissue maceration if the manipulation is not adequately performed with a sharp punch and delicate forceps. These problems tend to occur mainly in tumors that affect the eyelid margin[23].

Besides the presence of more than one tumor subtype in some cases, another factor that may contribute to non-agreement between biopsy and surgical specimen is the action of the inflammatory process following the first procedure, due to its immune response with lymphocytic infiltrate and apoptosis. Swetter et al showed that 24% of incisional biopsies that were positive for BCC and SCC showed no residual tumor after surgical excision of the lesion[14]. Holmkvist et al found signs of inflammation and scarring process in sections of MMS in lesions previously submitted to punch and shave biopsy. However, they found no evidence that this process had been responsible for the tumor eradication[25]. One should carefully select the biopsy site, preventing scabs, cracks, erosions, abrasions and ulcerations. For tumors from 1 to 4 mm in diameter, one should perform the biopsy in the center of the lesion or excise it completely. For larger sizes, one should select the edge, the more thickened area or the area with the more altered color, since these are the main features of the tumor.

Concluding, the 2-mm punch biopsy in two sites in cases of eyelid BCC allowed greater accuracy in the diagnosis of aggressive subtypes of this tumor when compared to its realization in one site, providing the surgeon with more appropriate surgical planning.

R E S U M O

Objetivo: comparar a acurácia da biópsia pré-operatória por trépano de 2mm em um sítio e em dois sítios no diagnóstico dos subtipos agressivos de carcinoma basocelular (CBC) palpebral. **Métodos**: os pacientes foram distribuídos aleatoriamente em Grupo 1 (biópsia em um sítio) e Grupo 2 (biópsia em dois sítios). Os resultados das biópsias foram comparados com o padrão-ouro (exame anatomopatológico da peça cirúrgica). A sensibilidade, especificidade, valor preditivo positivo, valor preditivo negativo, precisão e coeficiente Kappa foram calculados para determinar o nível de concordância nos dois grupos. **Resultados**: foram analisadas 105 lesões (Grupo 1: n = 44; Grupo 2: n = 61). A concordância foi de 54,5% no Grupo 1 e 73,8% no Grupo 2 (p-valor = 0,041). Não houve diferença significativa entre os grupos quanto à distribuição das variáveis quantitativas e qualitativas (sexo, idade, duração da doença, maior diâmetro do tumor, área e comprometimento de margens). A biópsia em dois sítios mostrou duas vezes mais chance de concordar com o padrão-ouro do que a biópsia de um sítio. **Conclusões**: a acurácia e os indicadores de desempenho foram melhores para a biópsia por trépano de 2 mm em dois sítios do que em um sítio para o diagnóstico dos subtipos agressivos de CBC palpebral.

Descritores: Biópsia. Neoplasias Palpebrais. Eficácia

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