

# Value of Intraoperative Retakes During Standard Resection of Basal Cell Carcinoma (BCC) of the Head and Neck

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## Abstract

**Background:** The lowest recurrence rates for basal cell carcinoma are achieved by surgical treatment. Low rates of residual tumour in specimens after incomplete excisions plus intraoperative frozen section accuracy are the rationale for analyzing the value of intraoperative re-excisions during basal cell carcinoma standard surgery.

**Objective:** To analyse intraoperative oncologic and cosmetic results of re-captures in patients surgically treated of basal-cells carcinoma. Secondary to analyse subclincic extention, the value of frozen intraoperative sections and reconstructive conducts employed. Setting: tertiary care Hospital of tumours.

**Methods:** Observational retrospective study. During 3-year period 84 tumours were resected. A comparative analysis in terms of recurrence, surgical defect and use of flaps was done between intraoperatively re-excised and not re-excised tumours.

**Results:** There were no statistical difference regarding recurrence rate and use of flaps. Mean surgical defect for re-excised and not re-excised specimens was 27,8mm and 22,8mm respectively, being the difference statistically significant ( $p=0.002$ ). Residual tumour was found in only 2,9% of re-excised specimens.

**Conclusions:** Re-excisions added on average 5mm to surgical defect per specimen and did not contribute to any benefit in terms of recurrence rates. A more conservative use of intraoperative re-excisions could improve functional and cosmetic outcomes.

**Keywords:** Basal-Cell Carcinoma; Relapse; Frozen Intraoperative Section

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## Introduction

CBC is the most common tumor in the human economy. As its registration in cancer databases is not mandatory, there are no exact data on its prevalence. However, in the literature there are different studies that account for the increase in its incidence in recent decades [1]. It represents at least 32% of all cancers and excluding melanomas, it occurs in 80% of skin cancers. In the US, 35% are diagnosed in white men and 25% in white women who will suffer from it at some point in their lives [1].

CBC appears when one of the basal cells of the skin undergoes a mutation in its DNA. Basal cells are found in the lower layer of the epidermis, which is the outermost layer of the skin. As new skin cells are produced, they push older cells to the surface, where they are shed.

The process of creating new skin cells is controlled by a basal cell's DNA, which contains the instructions that tell each cell what to do. The mutation tells the basal cell to multiply rapidly and continue to grow when it would normally die. Eventually, the abnormal cells that build up can form a cancerous tumor.

It often appears as a slow-growing, painless, shiny or ulcerated area

that can damage neighboring tissues without a tendency to spread or even cause death.

Risk factors are ultraviolet light, radiation therapy, prolonged exposure to arsenic, and lowered immune system.

8 histological subtypes are recognized: nodular, superficial, morpheiform (sclerodermiform), metatypical, micronodular, sclerosing, pigmented, and adenoid. The combination of subtypes is common; however, it must be accepted that the nodular and the superficial are the prevalent and least aggressive in exchange for the micronodular, metatypical and morpheiform ones, which are the most aggressive and with a greater tendency to recurrence.

Despite knowing other therapeutic options such as curettage, electrocoagulation, photodynamic therapy, laser therapy, cryosurgery, topical imiquimod or oral Vismodebig, the most effective treatment for BCC in terms of recurrence is surgical [2], either with standard resection or Mohs micrographic surgery. However, the latter is not available in most surgical centers in the country, in addition to being difficult in elderly patients, or those with comorbidities and in centers with limited surgical shifts.



In the literature there is evidence that what really matters during the resection of a BCC is to obtain a free margin, close or not of the tumor, which is supported by the high percentage of absence of residual tumor during margin enlargement surgery in Contact. There is also evidence to support the usefulness of intraoperative freezing.

The primary objective of this study is to analyze the impact of intraoperative retakes on the oncological and cosmetic results of patients operated on for BCC. As secondary objectives, it is proposed to analyze the subclinical extension, the value of intraoperative freezing and the reconstructive tactics used.

## Material and Methods

A retrospective, observational cohort study was conducted. Only virgin or recurrent BCC patients operated with conventional resection were included, between June 2015 and June 2018 followed for a minimum of 2 years or until death. Recurrence was defined as the appearance of a new lesion less than 5mm from the previous scar, confirmed by histopathological analysis.

The morphological characteristics of the lesions were obtained from the review of medical records.

The maximum subclinical extension (ESC) of each tumor resulting from the difference between the marked resection margin and the histological margin was measured.

The primary defect refers to the diameter of the primary resection specimen that results from the sum of the tumor diameter and twice the marked margin. For example, for a 10mm lesion resected with 5mm margins, the primary defect is 20mm.

Retake defect refers to the transverse diameter of the defect obtained from the pathological report. The total defect is the sum of both defects.

The sample was divided into two groups, retaken and not retaken, and a comparative analysis was performed in terms of recurrence, total defect, and use of flaps. Fisher's exact test was used for recurrence analysis, Mann-Whitney U test for defect analysis, and Pearson's Chi-square test for flaps. The p value <0.05 was taken as statistically significant.

## Results

91 patients were operated on. 17 did not comply with the proposed minimum follow-up period and were therefore excluded. In total, 74 patients with 84 lesions are evaluated.

40 (54%) were female and 34 (46%) male. The mean age was 69 years.

The most frequent location was the nasal pyramid (46.4%) followed by the ear (11.9%), cheek (9.5%) and the eyelid (8.3%). 82% of the tumors were treatment-naïve (Table 1).

Of the histological subtypes, the most frequent pure form was nodular (31%) followed by cordon (16.7%). In coexistence with other histological patterns, the nodular form had a prevalence of 46% and the cordoned of 32%.

Retakes were performed in 35 (41.7%) of the lesions, and residual tumor was found in only 1 (2.9%) of them (Table 1).

The comparative data between the group with resumption and without resumption are shown in Table 2.

**Table 1:** Population data.

VARIABLE	
AGE (mean and SD)	69 (11.42)
SEX	
Feminine	54%
Male	46%
HT	33%
DBT	13.1%
YO SOY	3.6%
VIRGINS (% , n)	82% (69)
LOCATION (% , n):	
Nose	46.4% (39)
Ear	11.9% (10)
Cheek	9.5% (8)
Eyelid	8.3% (7)
Lip skin	6% (5)
Forehead	6% (5)
Pre-ear	3.6% (3)
Scalp	3.6% (3)
Chin	2.4% (2)
Neck	2.4% (2)

SD: standard deviation; HT: arterial hypertension; DBT: diabetes; AMI: acute myocardial infarction.

**Table 2:** Recurrence, defects and reconstructive tactics.

	RETURN	NO RETURN	p value
Recurrence (% , n)	2.9% (1)	2% (1)	1
Defect (in mm)	27.8	22.8	.002*
Flaps (%)	60%	51%	0.415

\*Statistically significant

The total recurrence rate was 2.4%. For the recurrent lesions, it was 2.9% and for those without recurrence it was 2%, the difference being not statistically significant (p = 1).

The average size of the defects was 24.9mm. For the reoccurring lesions it was 27.8 mm and for those without re-taking 22.8mm, the difference being statistically significant (p = 0.002) (Table 2). There were two orbital exenterations (one in each subgroup) that were excluded from the defect analysis due to its three-dimensional complexity and because it was not based on size but rather on invasion of intraorbital structures.

Reconstruction using a local flap was performed in 55% of all lesions, in 60% of those retained, and in 51% of those without retakes, although this difference was not statistically significant. The most used flap was the indiano (28%) followed by the advancement flaps (25.5%) (Table 3).

The percentage of resections with free margins was 98% for lesions without retakes and 100% for retained lesions. In the last subgroup, in 11.4% of the lesions free margins were reached due to the retakes.

The mean subclinical extension was 1.85mm. No statistically significant correlation was found with tumor size (p = 0.49) or association with the presence of aggressive histological subtypes (p = 0.77).

Regarding intraoperative freezing, the sensitivity, specificity, negative predictive value, positive predictive value and false negative rate were 75%, 94.9%, 98.7%, 43% and 1.3% respectively.

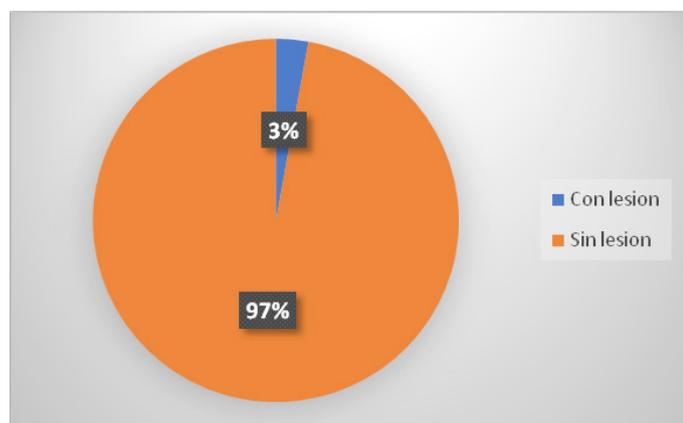
The mean follow-up was 33 months (range 11-59).



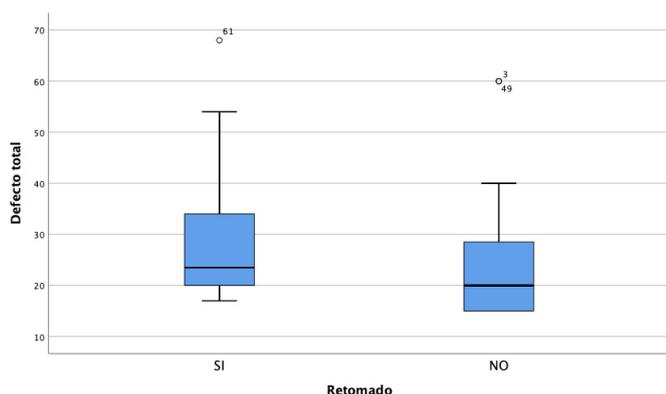
**Table 3:** Reconstructive strategies.

Reconstruction	Injuries
Primary closure	28 (33,3%)
Granulation	4 (4,8%)
Graft	6 (7,1%)
FLAPS (n,%):	46 (54,8%)
Indian	13 (28%) *
Advance	12 (25,5%) *
Nasogenian	6 (12,8%) *
Bilobed	3 (6,4%) *
Glabellar	3 (6,4%) *
Limberg	2 (4,3%) *
Mustarde	2 (4,3%) *
Temporary	2 (4,3%) *
Karapandzic	1 (2,1%) *
Front side	1 (2,1%) *
Burrowwebster	1 (2,1%) *

\*Frequencies of each flap expressed in relation to the total number of flaps performed (n=47).



**Figure 1:** Presence of injury in retakes.



**Figure 2:** Comparison of defects between both subgroups.

## Discussion

Much of the DNA damage in basal cells is known to result from ultraviolet (UV) radiation, which is found in sunlight and commercial tanning lamps and tanning beds. But exposure to the sun does not explain the cases of skin cancer that manifest on skin not commonly exposed to sunlight. There are other factors that can contribute to the risk and development of basal cell carcinoma, and the exact cause may not be clear in some cases.

There are yes, and the factors that increase the risk of contracting BCC are widely known, such as chronic sun exposure, radiation therapy, fair skin, advanced age, personal or family history of skin cancer, immunosuppressive medications, exposure to arsenic and xeroderma pigmentosum.

In the series presented, a recurrence rate of 2.4% has been found, which is in agreement with the 2-8% reported and the difference between the subgroup of retaken and that of not retaken was not statistically significant ( $p = 1$ ). Risk factors for recurrence could not be established, probably due to the small sample size [3,4].

The recommendation guide of the “National Comprehensive Cancer Network (NCCN) has established as recurrence factors the location, size, edges of the lesion, recurrent lesions, immunosuppression, previous radiotherapy, aggressive histological subtypes such as sclerodermiform, micronodular, metatypical, infiltrative, with ulceration and perineural invasion [5-10]. According to this stratification, 93% of the tumors in the analyzed sample were high risk.

Size is a proven risk factor for recurrence, although there is no consensus on the cut-off point to use. Bogelund FS, et al. (2007) [11], in a retrospective study of 1016 patients, it was found that T2 lesions > 20mm according to the TNM of the AJCC, have twice the risk of recurrence than T1 lesions.

The risk according to anatomical site has been extensively studied by Silverman MK, et al. (1999) [12] with 2,314 CBCs over more than 25 years at New York University School of Medicine. He grouped the locations into 3 risk categories, with statistically significant differences by multivariate analysis: high (nose, nasolabial fold, chin, jaw, perioral, periocular, ear), medium (scalp, forehead, pre and retro atrial, cheek) and lower (neck, trunk, extremities). As an additional data, he found that, within the medium-risk group, those lesions <10mm have a lower recurrence rate. The nose is not only one of the aesthetic units most frequently affected by CBC, consistent with 46% of nasal lesions in the sample presented, but it is also attributed the highest rates of recurrence [13,14].

Perineural invasion is the only route of dissemination of CBCs. Despite being low, its incidence occurs in around 2% of cases and has been associated with tumors > 2cm, aggressive histological subtypes and greater subclinical extension, and is an indication for adjuvant radiotherapy [15-17].

Regarding the higher recurrence rate in recurrent lesions, the subsequent development of a more aggressive histology and inadequate resection margins have been established as the cause, but not age and sex, although the latter is recognized as a recurrence factor in some series, there is little consensus in the publications [18-21].

The ESC of the CBCs is the rationale for resecting the tumor along with apparently healthy skin. Breuninger studied the same in more than 2000 CBCs and found that in recurrent tumors and in fibrosing (sclerodermiform) it is double, and increases with tumor size. Wolf and Zitelli, from Pittsburg U., carried out the work that is cited as a foundation by the main international guidelines to make recommendations on margins in CBC [22,23]. They determined by Mohs surgery that ESC is significantly higher in tumors > 2 cm. In smaller tumors, they demonstrated that ESC does not vary significantly with tumor diameter and that it is <4mm in 98% of cases, in agreement with 95% of the present sample. It is prudent to clarify that these authors do not refer to tumor histology in the cases they studied, and knowing that they only included tumors with clinically defined



borders, it is unlikely that they have analyzed aggressive histological subtypes. Salasche SJ, et al. (1981) [24], already in the 1980s they found that the average ESC of 51 morpheiform CBCs was 7.2mm and more recent works using the Mohs technique have confirmed these findings [24-26]. In this work, no association was found between aggressive histology and ESC.

1.3% of resections with margins in contact in this sample is <24% published in the literature [27]. An explanation for this finding could be that resection margins of 5-10mm were used, wider than the 3-4mm of other work groups. The only incomplete resection occurred in the group of lesions without retake. In the group of retaken lesions, there were 4-11.4% - lesions with margins in contact in the deferred report of the main piece without retake, and the performance of retakes avoided all of these potential incomplete resections.

Factors for incomplete resection include some locations such as the nose or eyelid and the presence of aggressive histology such as sclerodermiform and multifocal pattern [28-31].

The most important recurrence factor once the patient has been operated on is the compromise of the margins. The Royal College of Pathologists recognizes the difference between involved, uninvolved at <1mm, and uninvolved at > 1mm based on the low probability of recurrence when the tumor is more than one high-power field (400x) [32]. These findings had already been raised by Pascal et al. in the 1960s, when histopathological analysis techniques were less accurate than current ones, establishing that when the tumor is <0.5 mm or a high-magnification field, the recurrence margin is 12% vs. 33% when the margin is involved [33]. In the same vein, Dixon et al. found an average margin distance of 0.313 mm among recurrent tumors and 0.843 mm among non-recurrent tumors [14]. The UK Guidelines are very clear on this: in non-infiltrative lesions <2 cm the margin should be 4-5 mm. Smaller margins (2-3 mm) are an option in limited sites or when reconstruction is delayed [34].

The recurrence rate for incomplete resections is in the order of 30% and the course of action represents a dilemma for many surgeons [35]. Some argue that it is acceptable to observe these patients and others recommend reoperation because the recurrence rate in these cases is similar to that of a complete resection achieved during the first surgery or that local control of the disease may be compromised or be technically more complex if clinical recurrence is expected [36-40].

There are three main reasons why a resected lesion with compromised margins does not recur: regression induced by the immune system (CD3 and CD4 lymphocytes, IL-2) or by the healing process, spontaneous regression and that the margin has exactly passed through the end of the tumor [37,41-43]. The latter is compatible with the previously mentioned finding of the absence of residual tumor in the reappearances of the lesions with contact margins. The incidence of residual tumor during margin enlargement surgeries varies between 7-69% detected by Mohs micrographic surgery [44,45]. Regarding location, there is no consensus in the literature. While some retrospective studies find a lower presence of residual lesion in the nose, cheek and eyelid, others find these sites with a higher incidence of residual tumor [46-49].

Although this work does not attempt to analyze the incidence of residual tumor during a margin enlargement, it would not be illogical to suggest that the retakes in the 4/35 lesions with contact margins in the main tooth would be equivalent to margin enlargements. No residual lesion was found in any of them.

The truth is that of the total of lesions retaken (n = 35) only residual was found in one, which was a microscopic focus. By eliminating the possibilities of tumor regression previously described, it could be assumed that the only residual lesion would have resulted in a clinical recurrence and then the reoccurrences would have prevented 1 / 35-2.9% of recurrences in the subgroup of recurrent lesions.

Regarding intraoperative freezing, the sensitivity, specificity, negative predictive value and positive predictive value were 75%, 94.9%, 98.7% and 43% respectively. Although the sensitivity is moderate, in clinical practice the negative predictive value becomes more relevant and it was high, which is consistent with the low percentage of false negatives found (1.3%). The data in the literature are variable due to the different freezing techniques used and the different parameters reported.

Moncrieff MD, et al. (2015) [49] reported a false negative percentage of intraoperative freezing of 28.7% and therefore only proposed Mohs micrographic surgery. However, Bilden TT, et al. (2019) [50], In a retrospective study of 204 non-melanoma cutaneous carcinomas, found a percentage of false negatives of 2.45% for intraoperative freezing, a sensitivity of 89.79%, a specificity of 99.35%, a PPV of 97.78% and a NPV of 96.85%. Even more favorable results reported by Kedilioglu MA, et al. (2018) [51] that studied more than 1,300 CBCs, with percentages of sensitivity and specificity of 99% and 98.7% respectively. Nicoletti G, et al. (2013) [52] they set out to analyze the usefulness of freezing biopsy through a retrospective analysis, and paradoxically found that the complete resection rate was higher in those lesions in which intraoperative freezing was not performed [52]. However, the author himself acknowledges the “relevant methodological defects”, derived from the selection bias typical of a retrospective analysis. When he analyzed the rate of complete resection for eyelid carcinoma, it was higher in those cases in which intraoperative freezing had been used. Ghauri RR, et al. (1999) [53] found an accuracy of 91.1% in the detection of tumor presence or absence in the margins. An interesting piece of data from this work was the correct evaluation of the margins by surgeons, with an accuracy of 91% [53].

Beyond the diversity of published results, it is extremely difficult to compare the usefulness of intraoperative freezing because not all centers use the same technique. For example, Nizamoglu M, et al. (2016) [54] and Castley AJ, et al. (2013) [55], agree that the certainty of intraoperative freezing is greater than 98% when a complete circumferential analysis of the margins is performed, which is known as “en face” margins or “complete analysis of peripheral and deep circumferential margins” (CCPDMA for its acronym in English) [54,55].

Interestingly, the two recurrences presented free margins both in the deferred report and in the freezing, and in one of them an intraoperative retake had been performed that resulted in no injury in the deferred report. It could be inferred that the recurrences were not related to the free margins or the performance of retakes. Possible explanations are that it was a second primary, that there were iatrogenic tumor implants, that the histopathological analysis was not very sensitive or that it was a multifocal tumor [56,57].

The distinction between recurrence and second primary is important and although there is no consensus, Griffiths RW, et al. (2005) [58] they approach the subject in an original way. Applies the concept of cancerization of the field that is already known for squamous carcinoma of the upper aerodigestive tract and suggests that it is more logical that a resected lesion with free histological margins of 1-2mm,



is more a second primary than a derived recurrence from undetected tumor cells or from a multifocal tumor.

The size of the surgical defects was significantly greater in the group with retakes, which correlates with the greater use of flaps (60%) compared with the lesions without retaking (51%). Given that the size of the retakes was obtained from the pathological reports since they are not measured during surgery, it is likely that they were larger due to the "shrinkage" of the piece, estimated at around 15% for the width, 17% for the length and 29% for the area [59].

Assessing the cosmetic impact is complex. A priori, it is logical to think that the greater the defects, the greater the probability of requiring flaps to reconstruct them, which, unlike a primary closure, have a higher rate of complications (for example, ischemia and loss of them) and sometimes require more than one procedure such as pedicle section or thinning. In that sense, saving tissue through a more conservative use of retakes would be beneficial. However, the decision to make a flap also depends on the characteristics of the patient such as flaccidity, dermatological pathologies and tumor location. For example, a primary closure of a small periocular defector of the nasal wing can produce sequelae such as ectropion or elevation of the nasal wing, much more important than an aesthetic defect created by a flap.

Based on the most important findings of this study, absence of injury in 97% of the recurrences, similar recurrence rate between both subgroups, a significantly larger defect size in the group of recurrences, a priori it could be inferred that there is no need to perform retakes. However, under this scenario, we would have found 4 injuries with margins in contact that would have required surgery to widen the margins, even though it is known retrospectively that there was no injury in said reoccurrences. Retakes are then valued according to the reports of freezing, which despite the variability of results, most coincide in their use when Mohs micrographic surgery is not performed. It was analyzed in the retake group what the results would have been in terms of recurrence and surgical defect had they performed intraoperative retakes only in case of contact margin during freezing. The recurrence would have been 5.7% vs 2.9%, which is in agreement with the rates published in the literature, and the average defect was 24.5mm vs 27.8mm.

Although the principle of "first the oncological result, then the functional and finally the aesthetic one" is valid in oncological surgery in BCC, it seems to be of less importance in the sense that the recurrence rate in itself is very low, the The metastasis rate is around 0.1% and the specific mortality is practically nil [60]. No patient in the sample presented died of the disease, data that are consistent with the literature. Furthermore, the vast majority of recurrences can be controlled with resection under local anesthesia, achieving excellent local control of the disease.

Finally, the recommendations of the most relevant consensus guidelines are briefly summarized. Both the NCCN and the American Dermatological Association guidelines recommend standard resection with a 4mm margin for low-risk tumors, based on the aforementioned work by Wolf and Zitelli [7,23, and 61]. For high-risk tumors or those requiring delayed reconstruction, they recommend Mohs micrographic surgery or, failing that, standard resection with "wider margins" and repair with primary closure, by second intention or graft until the delayed pathological result. The European Consensus on the Diagnosis and Treatment of BCC recommends standard resection with a 3-4mm margin for low-risk tumors and Mohs surgery or standard resection with 5-15mm margins for high-risk tumors [62]. The best evidence

for the superiority of Mohs surgery over standard surgery comes from a randomized clinical trial with 10 years of follow-up by van Loo E, et al. (2014) [63]. In this study, 408 high-risk primary BCCs and 204 relapsed that are high-risk by definition were included, which were randomized by a computer system to standard resection with a 3mm margin or to Mohs surgery with the same margin. Within the group of primary BCCs the recurrence rate was 12.2% for standard resection and 4.4% for Mohs. Although Mohs was superior, the difference was not statistically significant. Its usefulness is recognized in relapsed, high-risk BCC or located in areas limited to reconstruction. [15,16,26, and 44].

Within the group of recurrent BCCs, the recurrence rate was 13.5% for standard resection and 4.9% within 40 months for Mohs surgery, this difference being more significant in the infiltrating subtype or in lesions that require several layers of resection [15,16].

The limitations of this study are recognized as its retrospective nature, the small sample despite the high prevalence of the disease and a limited follow-up period that could underestimate the recurrence rate. In reference to the latter, Rowe DE, et al. (1989) [64], calculated the cumulative rate at which recurrences appear for each year of post-treatment follow-up: first year 30%, second year 50%, third year 66%, fourth year 74%, fifth year 82% and 6-10 years 100% [64].

## Conclusion

In terms of recurrence, intraoperative retakes did not provide significant benefit, but prevented 11.4% of incomplete resections that would have implied a new surgery to widen the margins.

On the other hand, they created an additional 5mm defect per injury, which in the face region has a greater impact than in other areas of the body.

In a scenario where the performance of Mohs surgery is difficult (elderly patients with comorbidities and limitation of surgical shifts), a more rational use of intraoperative retakes could be made, saving healthy tissue, perhaps avoiding the need to perform flaps and maintaining an acceptable rate of recurrence with standard resection.

A prospective study with a larger number of patients and a longer follow-up period is proposed in order to confirm the trend observed in this work.

## Declarations

The authors declare that they have no conflicts of interest of any kind, that the work has been approved by the ethics committee responsible for the workplace and do not declare means of financing the work carried out.

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