

CONTROVERSIES IN DERMATOLOGY

Management of Basal Cell Carcinomas With Positive Margins

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Abstract. A common problem in day-to-day practice is the approach to take following resection of basal cell carcinoma with positive margins. In such cases, it is important to decide whether we should take a wait-and-see approach or consider re-excision or radiotherapy. To make this decision, 4 key points need to be clarified: the significance of positive margins; whether positive margins are equivalent to tumor persistence; whether negative margins equate with complete excision; and the rate of recurrence in cases of re-excision compared with those in which a wait and see approach is taken. Having addressed each of these points, the approach will depend on the characteristics of the individual case. Based on the evidence presented, an aggressive approach involving re-excision would seem indicated in aggressive cases, whereas a flexible strategy combining observation, surgery, and radiotherapy (or other treatments) can be used in less aggressive cases.

Key words: basal cell carcinoma, treatment, surgery, cancer, skin.

ACTITUD ANTE LOS EPITELIOMAS BASOCELULARES CON BORDES AFECTOS

Resumen. Un problema habitual en la práctica diaria es la actitud que debemos adoptar tras la resección quirúrgica de un epiteloma basocelular con afectación de alguno de los bordes. Que tipo de actitud debemos adoptar en estos casos: ¿observar?, ¿reextirpar?, ¿radiar? Para responder, en el artículo se desgranar una serie de conceptos: cuál es el significado de bordes afectos; ¿es equivalente borde afecto a persistencia tumoral?; ¿es equivalente borde libre a extirpación tumoral completa?; cuál es el porcentaje de recidivas al comparar la reextirpación y la observación.

Después de aclarar cada una de las preguntas, la respuesta sobre qué actitud tomar depende de las características de cada caso. Con las evidencias que se presentan parece indicada una actitud agresiva de reintervención en los casos graves y una estrategia flexible que combine la observación, la cirugía y la radioterapia (u otros tratamientos) en los casos menos agresivos.

Palabras clave: epiteloma, basocelular, tratamiento, cirugía, cáncer, piel.

Introduction

Although a broad therapeutic arsenal for treatment of basal cell carcinoma is currently available, surgical excision remains the gold standard for assessing the efficacy of other approaches. And this is where the problem lies, because the effectiveness of surgical treatment depends on numerous factors that hinder performing the randomized clinical trials needed to obtain unequivocal results. A recent systematic evidence-based review of treatment of basal cell carcinoma

by Smeets¹ is titled “Little evidence available on treatments for basal cell carcinoma of the skin.” In that review, based in turn on a review by Bath-Hextall et al,² the author only found 1 well-conducted randomized controlled study that compared recurrence of this type of tumor 3 to 5 years after 2 different therapeutic approaches (surgery and radiotherapy). The conclusions of that study indicated that there was some evidence that surgical excision is more effective than radiotherapy in the treatment of basal cell carcinoma. What is surprising though is how little evidence is available to guide the treatment of this the most common skin tumor. We should also mention that there are excellent studies that, although they do not meet such strict criteria, can point us toward answers to questions about the treatment of these tumors. One of these questions—and a common one—is the approach to take after surgical excision of basal cell carcinoma if the pathologist reports positive margins. We shall illustrate this with 2 examples of possible approaches (the first aggressive the second conservative)

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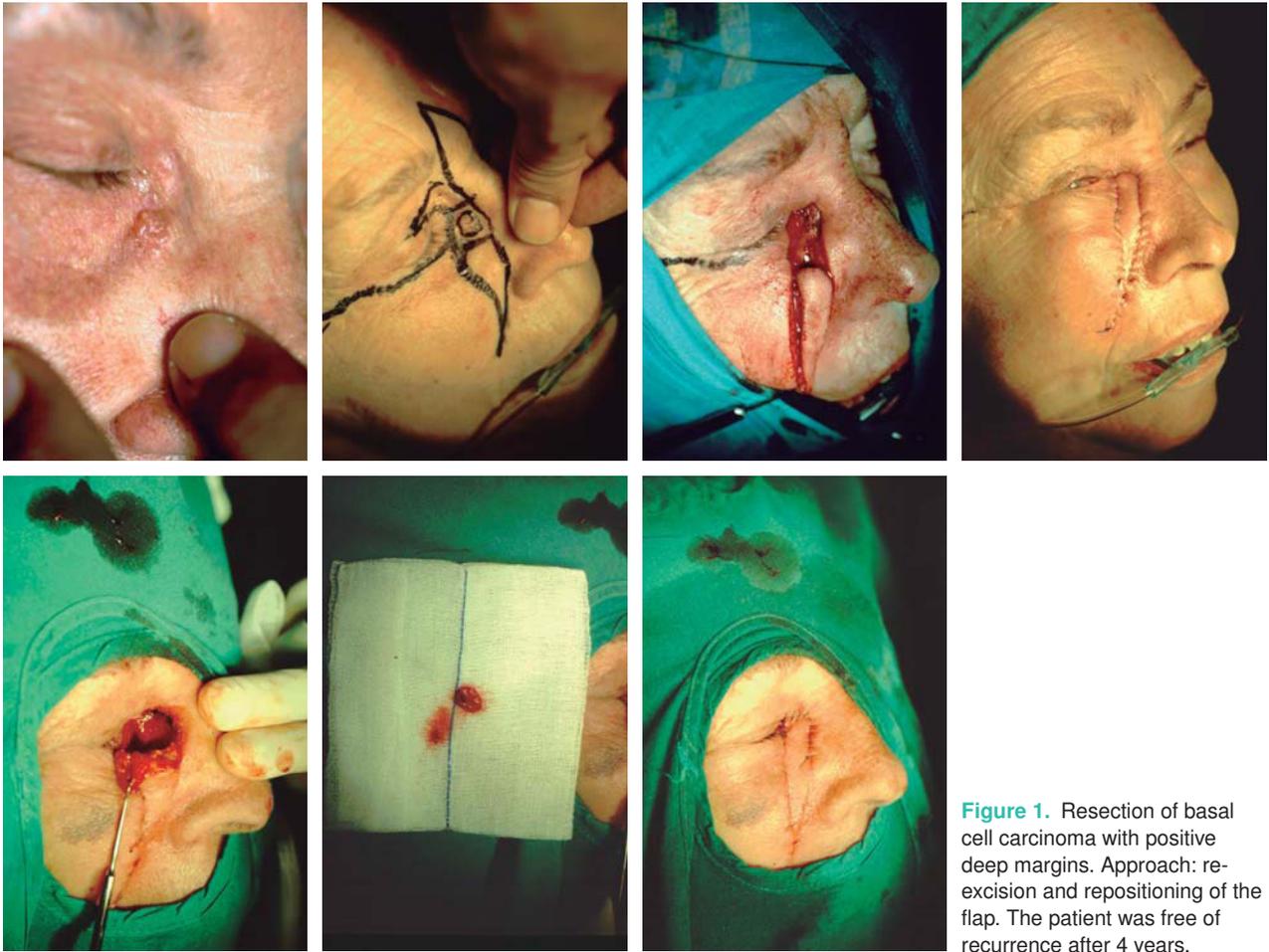


Figure 1. Resection of basal cell carcinoma with positive deep margins. Approach: re-excision and repositioning of the flap. The patient was free of recurrence after 4 years.

with similar outcomes in this case. The first example concerns a woman with infiltrative basal cell carcinoma of the medial canthus of the eye. After excision of the lesion, the pathology report indicated a positive deep margin. It was decided to raise the flap and resect the deep margin (Figure 1). No tumor cells were found in the histological study of the re-excised tissue. The second example concerns a female patient with infiltrative basal cell carcinoma of the lower eyelid (Figure 2). In the pathology report after excision, lateral and superficial involvement was reported in the upper outer region. The options were discussed with the patient and her family, and a wait-and-see approach was decided on. Four years later, neither of the women has suffered a recurrence. In such cases, it is important to decide whether we should take a wait-and-see approach or consider re-excision or radiotherapy.

The decision on whether to re-excite or not in basal cell carcinoma with positive margins can be framed within 4 key points that need to be addressed:

1. What is the significance of positive margins?
2. Is a positive margin equivalent to tumor persistence?

3. Do negative margins equate with complete excision?
4. What is the recurrence rate with a re-excision strategy compared to a wait-and-see approach?

What is the Significance of Positive Margins?

Abide et al³ interviewed a number of surgeons and pathologists to find out their opinions on status of surgical margins. The investigators asked 11 pathologists how they processed the tumor specimens and what they considered as “close” when describing margins. They also asked 25 plastic surgeons who use the information from pathology reports how the findings affected their approach towards the tumor. The answers suggested that processing of the samples varied a great deal even within the same hospital. The definition “close” to the margins encompassed the presence of tumor cells at between 0 mm and 5 mm from the surgical margin. Surgeons replied that their reaction differed according to whether the report included the terms “close to the margins” or “positive margins.” They tended

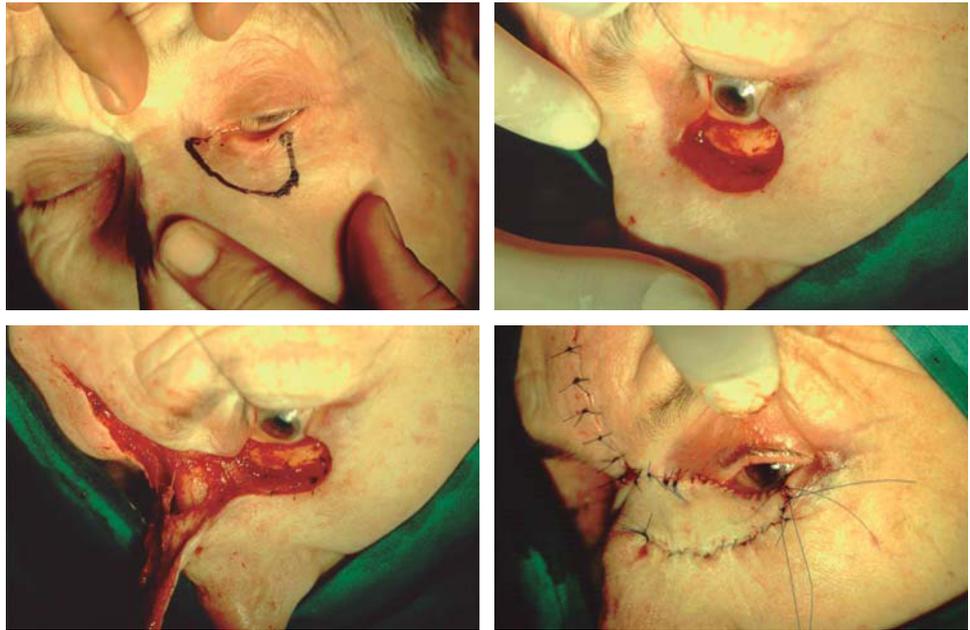


Figure 2. Resection of a basal cell carcinoma on the lower eyelid with superficial tumoral involvement of the outer margin of the surgical piece. Conservative approach: wait and see. The patient was free of recurrence after 4 years.

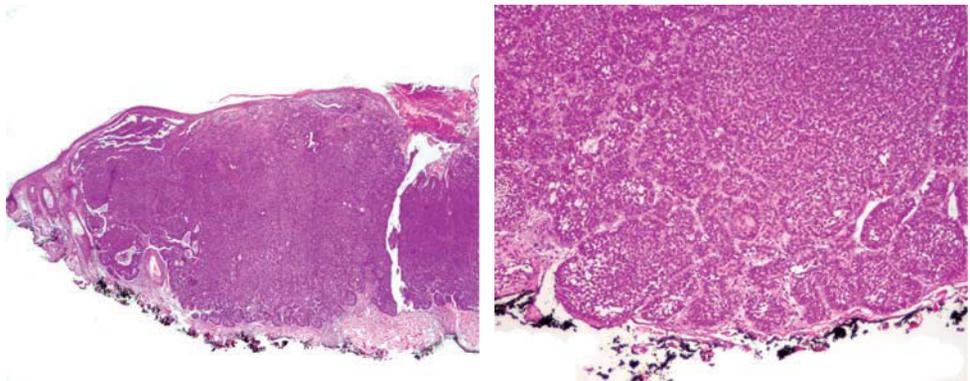


Figura 3. Basal cell carcinoma with expansive growth pattern. Despite being very close to the margins, the tumor is contained in a pseudocapsule, allowing the pathologist to report negative margins. Hematoxylin-eosin, $\times 20$ and $\times 100$.

to follow a wait-and-see approach for “close to the margins” and re-excision in the case of “positive margins.”

In a study of whether or not re-excision should be performed in basal cell carcinoma with positive margins, Griffiths⁴ found that anatomical and pathologic criteria for defining “incomplete excision of basal cell carcinoma” may not be the same between different studies, and they might not even be uniform within the same study. Furthermore, there is no consensus among dermatopathologists on the meaning of positive margins—different pathologists may report different findings. Likewise, the same pathologist may use different criteria according to the histological type of the carcinoma. This is reasonable, since, as shown in Figure 3, a basal cell carcinoma with expansive growth, despite being very close to the margins, is contained in a pseudocapsule, and that allows the pathologist to report a finding of negative margins. In contrast, an infiltrative basal

cell carcinoma, such as the one in Figure 4, has a stroma so characteristic of basal cell carcinoma that this alone is sufficient to report positive margins.

Is a Positive Margin Equivalent to Tumor Persistence?

Some authors affirm that the only way to ensure that tumor persistence does not occur in the event of positive margins is to re-excision and prepare serial sections of the specimen to identify residual tumor. Sarma et al⁵ were the pioneers of this idea and found 3 cases of residual tumor among 43 (7%) cases of positive margins. Subsequent analyses in similar studies have found rates of residual tumor varying between 7% and 45%, with a mean of 33% (Table 1). When Bielej et al⁶ performed Mohs surgery in 78 tumors with

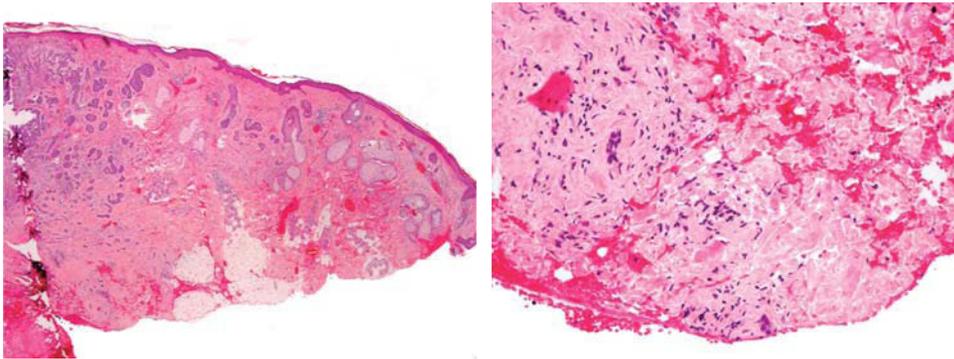


Figure 4. Basal cell carcinoma with an infiltrative pattern. The presence of stroma characteristic of basal cell carcinoma in the margin is sufficient for the margins to be reported as positive.

Table 1. Residual Tumor After Re-excision of Basal Cell Carcinomas With Positive Margins (Not Including Series of Mohs Surgery Because the Specimens Were Not Serially Sectioned)

Authors, y	No. of Basal Cell Carcinomas	Residual Basal Cell Carcinomas
Sarma et al, ⁵ 1984	43	7%
Griffiths, ⁴ 1999	74	45%
Bogdanov et al, ³⁵ 2001	100	28%
Hallock and Lutz, ²⁰ 2001	34	32%
Wilson et al, ¹⁹ 2004	84	45%
Griffiths et al, ²⁸ 2007	80	37.5%
Total	335	33%

positive margins, 55% of cases required a second Mohs procedure. The minimum residual tumor rate was therefore 55%. A study of all 850 basal cell carcinomas resected in 2003 by the dermatology service of our hospital, the Hospital Universitario de la Princesa in Madrid, Spain, showed that 52 (6%) had positive margins. After re-excision, the presence of residual tumor was demonstrated in just 11 cases (21%). The reasons why residual tumor was not found in all re-excisions could be as follows: first, that the tumor extended only to the margins without exceeding them; second, that residual carcinoma cells in the tumor bed perished and disappeared as a result of postoperative inflammation; third, that we were unable to identify tumor cells in the context of an inflammatory process; and, finally, that the tumor cells were not detected because the serial sectioning method was too coarse.

There is evidence to suggest that basal cell carcinoma may disappear after biopsy in 25% to 34% of patients.⁷⁻⁹ We know that substances that induce a T-helper-1 response, such as imiquimod and interferon- α , can cure low-risk basal cell carcinoma in a large number of patients. With topical irritants such as croton oil, rates of healing close to 25% can be achieved.¹⁰ It is also known that

immunosuppression increases the risk of developing biologically more aggressive cutaneous carcinomas. The immune system therefore seems to play an important role in the disappearance of residual tumor. In a study to evaluate the role of the acute inflammatory component in the disappearance of residual tumor, Spencer et al¹¹ performed curettage and electrocoagulation of 43 basal cell carcinomas of less than 1 cm in diameter (the expected recurrence rate at 5 years for this type of tumor is 8%-15% with this technique¹²). In 29 cases, re-excision was done immediately and tumor was found in 7 cases after serial sectioning of the specimen (corresponding to a cure rate of 75.9%). In 14 cases, the wound was allowed to heal and re-excision was done after 1 month; a tumor was found in 3 cases (corresponding to a cure rate of 78.6%). These differences were not significant, suggesting that acute inflammatory processes do not contribute to the disappearance of the residual tumor. In a subsequent study from the same group, re-excision was done 3 months after electrocoagulation.¹² As before, no significant differences were found with respect to immediate re-excision. Other theories to explain the apparent disappearance of residual tumor are based on the action of fibrosis, which might “strangle” the stroma needed for the neoplasm to develop.^{9,12,13}

Do Negative Margins Equate With Complete Excision?

In a review of 2900 patients with basal cell carcinoma treated between 1950 and 1960, Lauritzen et al¹⁴ found 101 recurrences after a mean follow-up of 5 years. Of these, 79 had undergone surgery. On review of the pathology reports from the initial excision, the authors found that 32 of these 79 cases (40.5%) had negative margins.

When a basal cell carcinoma is resected and sent to the pathology service for histological study, transverse sections are usually taken every 3 to 4 mm or using the quadrant method.¹⁵ There is no standard practice and the way in which specimens are processed may vary greatly from one laboratory to another. We know that with normal processing,

we can sample around 0.2% to 2% of the entire specimen. We therefore try to determine whether or not the tumor extends to the margins from this small sample of the specimen studied. But is this sampling really representative of the specimen as a whole? No study had been published on the sensitivity of normal pathology procedures to assess surgical margins in this type of tumor until a recent article by Kimyai-Asadi et al,¹⁶ who estimated the proportion of positive surgical margins that were not detected with transverse sections for evaluating surgical margins. Their method was ingenious: they collected 42 small (<1 mm) nonsclerosing well-defined facial basal cell carcinomas that were resected with a 2-mm lateral margin and that had positive surgical margins. After flattening the peripheral margins, they obtained frozen sections that were superimposed on transparencies with parallel lines spaced at 4-mm intervals. These lines represent the different transverse sections in a normal histological study of basal cell carcinoma of these characteristics. When the tumor intersected one of the lines, the section was classed as positive and would correspond to cases detected in a normal pathology study. When the tumor had no contact with the lines, it would not be detected by the normal pathology study (false negatives). The conclusions of the study were that conventional histological approaches in small and well-defined facial basal cell carcinoma resected with a 2-mm lateral margin have a sensitivity of 44% for detecting residual tumor in the surgical margins. In other words, the pathology report will indicate (in this type of tumor) that the surgical margins are negative in 56% of the tumors that actually have involvement of the margins.

The classic studies by Wolf and Zitelli¹⁷ and Breuninger¹⁸ showed that basal cell carcinoma resected with a 2-mm lateral margin have positive margins in 30% of the cases. These findings, in conjunction with those of Kimyai-Asadi et al,¹⁶ suggest that only 44% of this 30% will be detected by the normal histological study. Therefore, 17% of the tumors resected according to these criteria will be falsely identified as having tumor-free margins.

What is the Recurrence Rate With a Re-excision Strategy Compared to a Wait-and-See Approach?

In the studies reviewed, the recurrence rates of basal cell carcinoma associated with a wait-and-see approach after a finding of positive margins varied greatly (from 0% to 100%) (Table 2). However, to answer the above question we would need to undertake prospective, randomized clinical trials with a minimum follow-up of 5 years and 3 different arms: the first arm would examine the recurrence rate when the tumor is resected and the margins are negative according to the pathology report; the second would study the recurrence

Table 2. Recurrence After Positive Margins and a Wait-and-See Approach

Authors, y	No. of Basal Cell Carcinomas	Follow-up	Recurrence Rate
Pascal et al, ³⁶ 1968	42	10 y	33%
De Silva and Dellon, ³⁷ 1985	34	61 mo	41%
Nagore et al, ²¹ 2003	61	5 y	26%
Richmond and Davie, ²⁶ 1987	60	5 y	38%
Gooding et al, ²² 1965	66	5 y	35%
Friedman et al, ²⁴ 1997	15	4 y	100%
Hallock and Lutz, ²⁰ 2001	25	3.6 y	0%
Berlin et al, ³⁸ 2002	19	3.4 y	16%
Liu et al, ²³ 1991	67	32 mo	31%
Griffiths, ⁴ 1999	18	32 mo	0%
Wilson et al, ¹⁹ 2004	140	31 mo	21%
Spraul et al, ³⁹ 2000	49	31 mo	12%
Sussman and Liggins, ³¹ 1996	82	18 mo	30%
Total	704	>31 mo	26.9%

rate when the tumor is resected with positive margins and we decide to wait and see; and the third would assess the recurrence rate after re-excision in cases of positive margins (Figure 5). As we have been unable to find studies conducted according to this design, we will now discuss the 3 studies that we believe shed most light on the matter. In the study by Wilson et al¹⁹ (the largest series of resected basal cell carcinomas), the authors retrospectively reviewed 3795 basal cell carcinomas treated between 1990 and 1999: 3560 had negative surgical margins and a recurrence rate of 1% was reported at 31 months; 235 had positive margins, 84 of which were re-excised (without recurrence) and a wait-and-see approach was followed in the remaining 140, with a recurrence rate of 21% after 31 months (Figure 6). The authors were in favor of flexibility when deciding between repeat surgery or a wait-and-see approach. The second study, performed by Hallock et al,²⁰ was a prospective study with 3.6 years of follow-up in which a wait-and-see approach was taken in 25 patients with basal cell carcinomas with positive margins

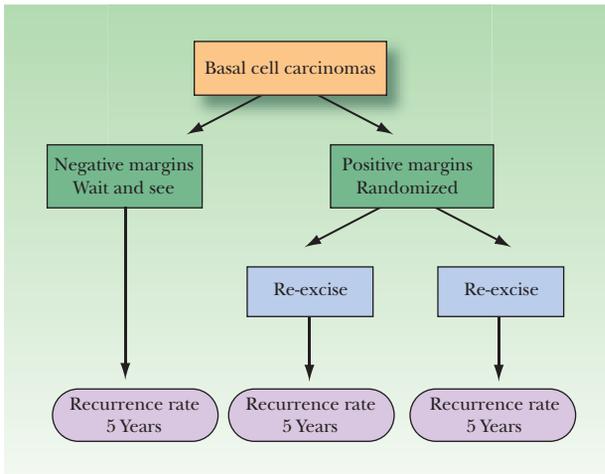


Figure 5. Suggested overview of a prospective randomized clinical trial with at least 5 years of follow-up.

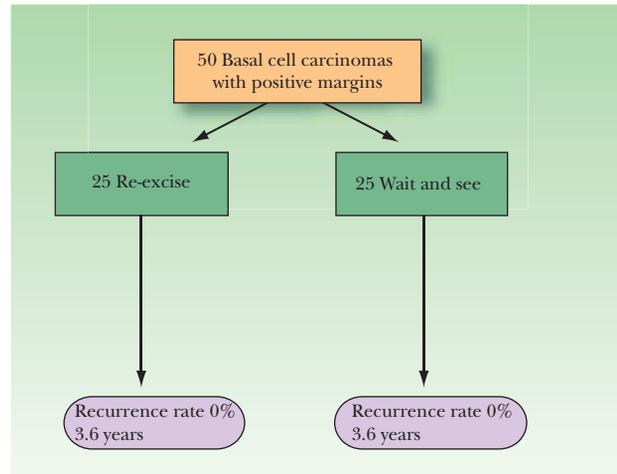


Figure 7. Source: Hallock et al.²⁰

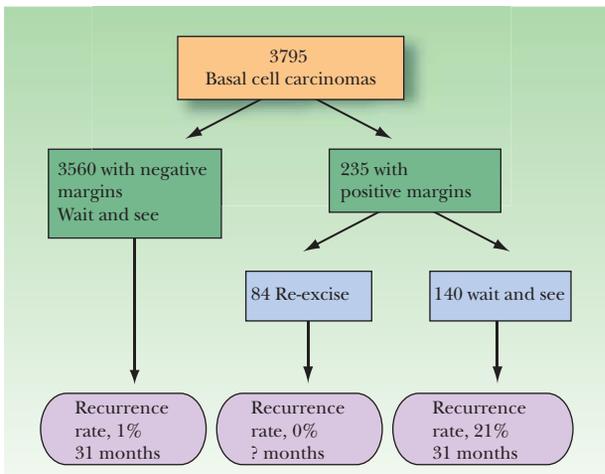


Figure 6. Source: Wilson et al.¹⁹

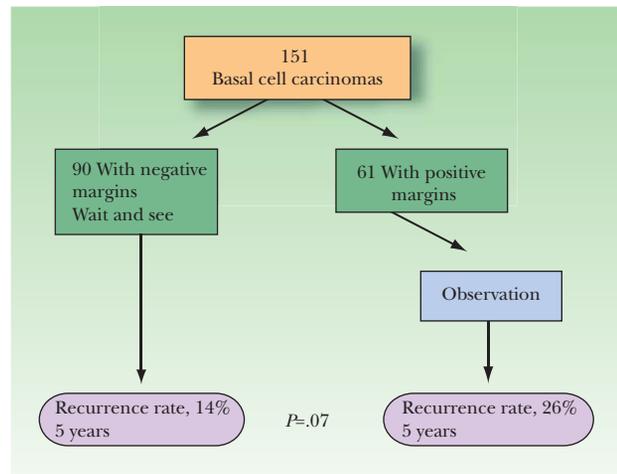


Figure 8. Source: Nagore et al.²¹

and the remaining 25 underwent a repeat procedure (Figure 7). The recurrence rate was 0% in both groups. The third study was carried out in Spain by Nagore et al,²¹ who reviewed the disease course of 151 basal cell carcinomas treated with surgery and with a minimum follow-up of 5 years (Figure 8). In 90 cases, the margins were negative and the recurrence rate in this group was 14%. In 61 cases, the margins were positive and the recurrence rate was 26%. However, these differences were not statistically significant.

Discussion

The most widely cited article, and the one on which most authors who advocate wait-and-see approach despite positive tumor margins base their rationale, was published by Gooding et al²² in the 1965. A wait-and-see approach was

taken in 66 patients with positive margins and those patients were followed for at least 5 years. The recurrence rate was 34.8% (a figure which would decrease to 19% if patients who did not complete the 5 years of follow-up due to death or other reasons were not excluded). Patients with clinical recurrence successfully underwent surgery or radiotherapy. With these findings, the authors concluded that, in view of the indolent nature of this tumor, when faced with the presence of positive tumor margins in the initial excision, it is preferable to wait and see and then treat only in patients with clinical recurrence.

In the event of positive margins, an alternative to re-excision is radiotherapy. Liu et al²³ studied 187 patients with basal cell carcinomas and positive margins. Of these, 120 underwent radiotherapy and 67 were put under observation. The recurrence rates at 32 months were 7/120 (6%) and 21/67 (31%), respectively. These second recurrences

were treated with radiotherapy and surgery and the authors reported no significant difference between the 2 groups for the probability of local control at 10 years (92% and 90%, respectively). A costs analysis showed that the option of directly treating those with positive margins represents a slightly lower economic burden compared to a wait-and-see approach and treatment of recurrences. However, in view of the side effects of radiotherapy, the authors concluded that the policy of monitoring and treating recurrences is the most appropriate for this type of patient.

The initially more aggressive approach of re-excising all lesions with positive margins is based on studies that showed high recurrence rates with the wait-and-see approach compared to almost no recurrences with excision. For example, Friedeman et al²⁴ studied 25 patients with basal cell carcinoma and positive margins after excision. After 4 years of follow-up, the authors found that of the 10 patients (mostly with a nodular pattern in the pathology study) who underwent a second procedure none had any recurrences, whereas the 15 patients (mostly with a sclerosing pattern in the pathology study) with the wait-and-see approach all finally suffered recurrences. These authors were in favor of immediate re-excision given that, for them, a recurrence rate of 30% was not acceptable and that the subsequent radical surgery needed to control the disease would not be the best option for the patient. Robinson et al²⁵ reviewed recurrences in patients who underwent Mohs surgery after excision with positive margins. They concluded that the wait-and-see approach led to very problematic recurrences and that immediate re-excision required less-extensive surgery.

Ambiguity is inherent in the answers to the questions that we have addressed in an attempt to resolve which initial approach to take, that is, whether or not to treat basal cell carcinoma with positive margins. For the first question about the definition of positive margins, the correct answer would be that this varies according to the pathologist and the type of basal cell carcinoma. For the second question about whether a positive margin equates with residual tumor, we can affirm that this is not the case in many patients (two-thirds according to Table 1). For the third question, about whether a negative margin is equivalent to complete tumor excision, the answer is no. For the fourth question, which compared the recurrence rate for re-excision and a wait-and-see approach, we can say that there are obviously more recurrences among patients with the wait-and-see approach (27% according to Table 2).

An aggressive treatment may not be appropriate in elderly patients or those in a poor state of health, particularly in the case of low-risk lesions. On the other hand, it seems reasonable to consider an aggressive approach in healthy young patients. We will now leave aside for a moment the characteristics of the patient and focus on the tumor characteristics, that is, we will analyze the characteristics indicative of a more aggressive tumor, in which a concerted

approach is needed. According to the data in Table 2, we see that recurrence after a finding of positive margins occurs in approximately 1 out of every 4 patients. The most logical approach would be to identify this subgroup of patients and treat them. To do this, we are going to analyze what makes these tumors more aggressive.

Site

Several authors agree that sites such as the nose or nasal ala are associated with a high risk of recurrence when the margins are positive.^{4,26} A recent meta-analysis of the studies published on this topic found that the relative risk of incomplete excision of basal cell carcinoma in the regions of the nose and ears was 2.24 times greater than that of the rest of the body.²⁷ Recent studies seem to show that the rate of incomplete excision is highest in the periorbital region,²⁸ although there are some discrepancies in the findings.

Positive Margins

Most of the studies reviewed report evidence that a positive deep margin is associated with recurrence.^{23,26} In contrast, the recurrence rate is much lower when it is the lateral margins that are positive.²³

Histology

The pattern of tumor growth in basal cell carcinoma is a significant factor in determining the recurrence rate. As shown by some authors, tumors with infiltrative or multifocal patterns have a significantly higher recurrence rate than nodular ones.^{26,29} In agreement with those findings, Breuninger and Dietz¹⁸ reported a study based on more than 2000 basal cell carcinomas. They found that the size, histological type, and recurrent tumors were factors that influenced the subclinical extension. They also showed that, in basal cell carcinoma, subclinical infiltration of the surrounding tissue occurs 3-dimensionally with contiguous and irregular finger-like protrusions. This histological appearance of recurrent basal cell carcinoma may differ (usually more aggressive) from that of the primary tumor in almost 20% of cases,³⁰ although some authors believe that this is due to healing changes and does not have any effect on the biological behavior of the tumor.¹³

Type of Closure

The method of closure does not have an effect on the recurrence rate, but closure using flaps delays recurrence.²⁶

Primary or Recurrent Tumors

The recurrence rate seems to be higher in tumors that are already recurrent than in primary tumors.^{18,26} Perhaps this group of recurrent tumors is the one that requires special attention, and the initial approach to be taken in such cases should be aggressive as these recurrences usually become untreatable tumors or tumors requiring very aggressive surgery that the patient is not always able to withstand.

Although these findings seem solid and logical, other authors do not find a relationship between recurrence of tumors with positive margins and site of the positive margin, histology, prior treatment, or tumor site.³¹

A wait-and-see approach might be the most appropriate in small primary basal cell carcinomas that have positive lateral margins, occur at sites other than the ears or the centre of the face, and have a nodular or superficial histology, and in elderly patients with multiple complaints or a short life expectancy. In contrast, re-excision seems to be most appropriate in high-risk recurrent tumors that meet one or more of the following criteria: tumors located on the ears or center of the face, greater than 2 cm in diameter, recurrent lesions, previously treated by radiotherapy, and tumors comprising aggressive histological types including perineural, periadnexal, or perivascular invasion and tumors with an infiltrative appearance. Positive deep margins should also be considered for aggressive treatment.

The approach of a repeat intervention or monitoring according to how aggressive the tumor is supported by a number of clinical guidelines.³²⁻³⁴

Conclusions

Although no conclusive evidence is available, the studies analyzed and common sense suggest that a wait-and-see approach in patients with aggressive tumors may be risky and that a flexible approach that combines monitoring, surgery, and radiotherapy (or other treatments) may achieve good outcomes in less aggressive tumors.

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Conflicts of Interest

The author declares no conflicts of interest.

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