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Basal cell carcinomas of the eyelid: results of an initial surgical management¹

Carcinome baso-cellulaire de la paupière : résultats d'une prise en charge chirurgicale initiale²

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Running title :

Surgical management of basal cell carcinomas of the eyelid

Prise en charge chirurgicale initiale d'un carcinome baso-cellulaire de la paupière

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² Cette étude a fait l'objet d'une présentation au 123^e congrès annuel de la Société Française d'Ophtalmologie, en mai 2017.

ABSTRACT :

Purpose :

Our objective was to assess the results of surgical management of palpebral basal cell carcinomas (BCC) followed by a second line treatment discussed during a Multidisciplinary Team Meeting (MTM).

Materials and Methods :

This retrospective single-centred study includes all surgically-treated basal cell carcinomas of the eyelids between January 2005 and January 2015. After initial surgery, the cases were systematically discussed during a multidisciplinary team meeting in order to assess the need for additional treatment. Data relative to the patient, tumor and management were pulled from the medical record.

Results :

171 patients were included, with a mean age of 74 years. 151 patients underwent pentagonal resection of the tumor, and 20 patients had a superficial excision. After surgical management, 120 patients (70.2 %) were considered to have sufficient free margins. The other 51 patients (29.8 %) had insufficient margins due to remaining tumor cells (38 patients) or free margins less than 1 mm. Among these 51 patients with insufficient margins, 19 received a second surgical treatment, 17 patients received adjuvant radiotherapy, and 15 were followed closely with an intensive biannual follow-up program.

No patients were lost to follow-up. With a mean follow-up of 42 months (min. 6 months – max. 128 months), 7 out of 171 patients (4.1 %) developed a local recurrence. The mean time between surgical management and recurrence was 24 months. The recurrence rate was higher for the group of patients with a recurrent tumor (11.6 %) than for the group of patients referred for initial management (2.8 %). Incomplete resection was also associated with a

higher recurrence rate (3 recurrences out of 51 patients).

Discussion :

The management of basal cell carcinomas of the eyelid is first and foremost surgical with the goal of complete resection confirmed by histopathological analysis. The histological analyses (Mohs micrographic surgery, frozen section technic, paraffin fixation) and recommended sizes of the margins can vary in the literature, with recurrence rates from 1.8 % to 9.5 %.

Conclusion :

In our experience, multidisciplinary management of BCC of the eyelid, including initial macroscopic surgery, histopathological analysis stating the histological type and size of the margins, along with additional treatment discussed in a MTM, allows for a recurrence rate of 4.1 %.

Key words :

Basal cell carcinoma ; eyelid ; oncology ; paraffin fixation ; multidisciplinary team conference, surgical treatment, histology

Résumé

Objectif

Notre objectif était d'évaluer les résultats d'une prise en charge chirurgicale de carcinomes baso-cellulaires (CBC) palpébraux, associée à un traitement de deuxième ligne discuté au cours d'une réunion de concertation pluridisciplinaire (RCP).

Matériel et Méthode

Cette étude monocentrique rétrospective inclut tous les CBC palpébraux traités chirurgicalement entre janvier 2005 et janvier 2015 à l'Institut Curie. Après la chirurgie initiale, tous les dossiers étaient discutés systématiquement en RCP afin d'envisager le recours à un traitement de deuxième ligne. Les données relatives au patient, à sa tumeur et à sa prise en charge étaient tirées du dossier médical.

Résultats

171 patients ont été inclus, avec un âge moyen de 74 ans. 151 patients ont bénéficié d'une résection pentagonale, et 20 patients d'une exérèse superficielle. Après la prise en charge chirurgicale, 120 patients (70.2 %) ont été considérés comme ayant des marges saines suffisantes. Les 51 autres patients (29.8 %) avaient des marges insuffisantes à cause de la présence de cellules tumorales ou bien à cause de marges saines inférieures à 1 mm. Parmi ces 51 patients, 19 ont bénéficié d'une reprise chirurgicale, 17 ont été traités par radiothérapie adjuvante et 15 ont été suivis de manière rapprochée avec un programme de consultations semestrielles.

Avec un suivi moyen de 42 mois (min 6 mois, max 128 mois), 7 patients (4.1 %) ont présenté une récurrence locale de CBC. La durée moyenne entre la chirurgie initiale et la récurrence était de 24 mois. Le taux de rechute était plus élevé chez les patients pris en charge pour des récurrences de CBC (11.6 %) par rapport aux premières localisations de CBC (2.8 %). Une résection

incomplète était associée à un taux plus élevé de récurrence (3 récurrences pour 51 patients).

Discussion

La prise en charge du CBC est avant tout chirurgicale, avec un objectif de résection complète confirmée par l'analyse histologique. Cette analyse anatomopathologique (Mohs micrographic surgery, examen extemporané des berges, fixation en paraffine) et la taille des marges saines recommandées peuvent varier dans la littérature avec des taux de récurrences de 1.8 % à 9.5 %.

Conclusion

Une prise en charge multidisciplinaire de CBC de la paupière, incluant une chirurgie d'exérèse macroscopique, une analyse histologique précisant le type histologique et la taille des marges saines, associée à un traitement de deuxième ligne discuté en RCP, permet, dans notre expérience un taux de récurrence de 4.1 %.

Mots clés :

Carcinome baso-cellulaire ; paupière ; oncologie ; fixation paraffine ; réunion de concertation pluridisciplinaire ; traitement chirurgical ; histologie

INTRODUCTION :

Basal cell carcinomas are the most frequent malignant tumours of the eyelid. The diagnosis of basal cell carcinomas is mainly clinical. In some cases, it may be necessary to perform a biopsy to confirm the diagnosis with a histological analysis. The first line treatment relies on a surgical procedure. When it comes to basal cell carcinomas of the eyelid, the main difficulty is to excise with sufficient margins without deteriorating the eyelid functions. Since BCC rarely metastasize, the main issue remains the recurrence rate. In order to improve the management of cancers, multidisciplinary team meeting (MTM) are now part of every standard oncology procedure. For patients suffering from a basal cell carcinoma of the eyelid, these meetings allow ophthalmologic surgeons, radiotherapist and anatomopathologist to discuss a second line treatment (radiotherapy, second surgery, intensive follow-up program) based on the result of the first line surgical management.

The main objective of the study was to evaluate the outcome of an initial surgical procedure of basal cell carcinomas of the eyelid, followed by a systematic histological analysis of the margins and eventually a second line of treatment discussed during a multidisciplinary team meeting.

MATERIEL AND METHODS :

The clinical records of 192 patients who underwent a surgical management of a basal cell carcinoma of the eyelid at Institut Curie Hospital, Paris, France between January 2005 and January 2015 were reviewed retrospectively. The Institutional Ethics Committee gave its approval for this research. This study was conducted in accordance with the declaration of Helsinki. After the MTM, several options were discussed, and every patient gave an oral consent after receiving both an oral and a written information.

Patients suffering from Xeroderma Pigmentosum (a genetic condition linked to an increase in the incidence of BCC) were excluded, as well as patients with a follow-up time below 6 months and patients who underwent a first line radiotherapy treatment prior to the surgical management.

For every patient, the clinical and the histological data from the medical record were collected. These data were i) for the patient : the sex, the age at diagnosis, the medical history of prior basal cell carcinomas ii) for the tumour itself : its exact location on the eyelid (upper or lower eyelid, external or internal canthus lesion) and the relation to the lid margin, the maximum diameter, the clinical type of basal cell carcinomas (nodular, sclerodermiform infiltrated, superficial), the number of previous recurrences. iii) for the surgery : the exact time of surgical management and the type of surgical procedure, iii) for the histological analysis : the analysis of the margins (on contact, at x millimetres of surgical beds) and the histological subtypes (nodular, sclerodermiform, infiltrated or superficial).

This histopathological differentiation distinguishes nodular, superficial and infiltrative BCC [1]. Micronodular BCC has been separately recognized as a high-risk subtype. Other less frequent subtypes of BCC have also been described.

The surgical procedure could consist of a classic pentagonal resection [2], or a simple superficial excision. Tumour margins were per operatively marked with care by the surgeon. All patients were categorized after their surgical management in one of two groups based on the tumour-free margins, assessed by the anatomopathologist after paraffin fixation.

The margins were considered sufficient if there was a minimum of 1 mm of tumour free margins for nodular BCC or more than 2 mm for other histological type of BCC. For this specific group of patients with sufficient free margins, was discussed a long term follow up program consisting of a consultation every 12 months.

The margins were considered too close in the following cases : i. there was a margin under 1 mm for nodular BCC, or ii. under 2 mm for other histological type of BCC and for recurrent BCC. For these patients were discussed a second line treatment (surgery, radiotherapy), or at least a more intensive, half yearly, long-term follow-up program.

Every case of BCC was discussed during one of the weekly ocular oncology MTM : for every patient was noted whether a second line treatment (surgery, radiotherapy or intensive half-yearly surveillance) or a normal yearly surveillance was decided.

The recurrence was defined as histologically-proved reappearance of the basal cell carcinoma. BCC on other regions of the eyelid, or even on the contralateral eyelid were recorded as new tumours and not as recurrences.

The main outcome measure was the recurrence rate.

Statistical analysis was performed using Microsoft Excel.

RESULTS :

Data were collected from 192 patients. 21 patients were excluded of the analysis based on the exclusion criteria : 16 of them had a follow-up time below 4 months (8/16 were only followed 2 months), 3 patients suffered from Xeroderma Pigmentosum, 1 patient was addressed after a first line radiotherapy of the eyelid, and 1 patient was exenterated as a first line treatment before being addressed to the hospital.

The population characteristics are listed (Table 1). The mean age at diagnosis was 74 years old (min 14, max 94). The sex ratio showed 63.7 % of women.

Amidst our patients, 26 (15.2 %) had a history of other cancer and 38 (22.2 %) had already suffered from a previous basal cell carcinoma in another localization.

In most cases the basal cell carcinoma was located on the lower eyelid (76.6 %) and the mean clinical size was 10,2 mm (3 mm-28 mm).

The mean time between diagnosis and surgery for the cohort of patients was less than 29 days.

151 patients (88.3 %) underwent a pentagonal resection whereas 20 patients (11.7 %) were treated with a superficial excision for BCC located far from the lid margin.

Regarding the histological subtype, 76 patients (44.4 %) presented with a nodular BCC whereas 55 patients (32.2 %) suffered from an infiltrated BCC. Superficial BCC and sclerodermiform BCC were observed each in 10 (5.5 %) and 30 patients (17.5 %).

The reconstruction procedure used mainly a simple temporal sliding flap (52.1 %). Direct stitching was preferentially used after superficial excision of small tumours (36.3 %). For 20 patients (11.7 %), nose cartilage strips were used to treat an extended eyelid defect.

120 patients (70.2 %) were considered to clear margins. 51 patients (29.8 %) had too close margins because of remaining tumorous cells or because of margins smaller than 1 or 2 mm (for high risk histological subtype).

After the MTM, 120 patients with sufficient margins were followed according to a yearly surveillance program (Table 2). The 51 patients with insufficient margins needed a second line treatment : 19 received a surgical therapy in order to provide larger tumour free margins, 17 patients received an adjuvant radiotherapy treatment : 8 of them were older than 80 years old and 4 patients had extended lesions of the medial canthus that would have needed a disfiguring surgery. 15 patients were closely followed with an intensive follow-up consultations program (half-yearly minimum), 7 of them were older than 85 years old, 2 patients could not receive a radiotherapy treatment because of the BCC was located near the lachrymal gland. Other patients refused radiotherapy or surgery and accepted the follow up program.

The mean follow-up time of the entire cohort was 42 months (6 – 128). 88 patients were followed more than 3 years and 45 patients had a follow up over 5 years.

Our primary end point was the recurrence rate. Overall only 7 patients suffered from a recurrence.

2.7 % of the patients presenting a first BCC suffered from a recurrence whereas 11.5 % of the patients addressed for a recurrent BCC suffered from another recurrence.

Amidst all the recurrences, the histological analysis showed 5 cases of infiltrated BCC and 2 cases of sclerodermiform BCC.

Each of the seven patients was offered a surgical management. 6 patients agreed to the surgery and 1 patient refused and was finally treated with radiotherapy.

The mean time between the initial surgical management and the recurrence was 24 months.

DISCUSSION :

BCC is a major public health issue with an incidence increasing over the years by a rate of 4 to 8 % [3]. Several risk factors have been linked to BCC epidemiology such as cumulative UV exposure and phototype [4] or immunosuppression[5]. Different genetic condition increasing the risk of skin malignancy have been described [6]. In this study 3 patients suffering from Xeroderma Pigmentosum were excluded to avoid confusion in the recurrence rate.

Our cohort showed some similarities with other studies. As described in the literature, most patients presented a nodular BCC [7] and a majority of BCC were located on the lower eyelid [8].

The histological analysis of the recurrences showed a majority of infiltrative BCC, a high-risk histological variants of BCC [9]. It is interesting to point out that a majority of BCC was considered clinically nodular, whereas the final histological diagnosis revealed another

potentially more aggressive subtype. It is difficult to find research exploring the correlation between the clinical aspect and the final pathological diagnosis. This highlights the importance of the histological analysis to accurately define BCC.

We collected data of a significantly high number of patients, considering this is a single centred study. 171 patients were included, with a maximum follow up time of 128 months. It would be interesting to keep following the cohort in order to improve the follow up time.

Surgery remains the first line treatment of BCC of the eyelid.

The HAS (French National Authority for Health) recommendations [10] provided some guidelines in the management of BCC. According to these recommendations, BCC of the eyelid have a high risk of recurrence. Primary nodular BCC under 10 mm have the best prognosis. In this case, strict clinical margins of 4 mm are necessary. Other palpebral BCC (sclerodermiform, superficial, nodular with a size over 10 mm, relapsing BCC) are considered of a worse prognosis, which indicates clinical margins of 5 mm minimum and up to more than 10 mm. However, these recommendations consider the clinical margins but does not specify the histological margin needed.

Even according to the National Clinical Guidelines [11] information on histological margins is more limited than clinical margins.

In the literature, different techniques have been described in order to manage BCC with minimum margins to avoid deteriorating the ocular palpebral function.

Several authors studied the Mohs Micrographic Surgery (MMS) [12]. The recurrence rate described can vary from 0.5 to 4 % for primary BCC to 2.9 to 10 % for recurrent BCC [13-15]. The MMS is mainly indicated in the management of high-risk BCC defined by the size and an aggressive histopathological subtype [16]. Although the MMS clearly seems to provide the least recurrence, its cost-effectiveness is still to debate [17-23].

Different techniques of Margin Frozen Section have been described [24], with recurrence rates reaching 4.7 % [20]. The downsides are the need of an available pathologist on site and the difficulty to read frozen section's samples with a non-negligible risk of false positive and false negative results when compared with paraffin fixation [22]. Overall, the Royal College of Pathologist suggests that frozen section should be limited to Mohs' micrographic surgery and its use for a specific clinical diagnostic problem usually shouldn't be supported [9].

The procedure used in this study was based on a first line surgery, followed by second line treatment depending on the histological subtype and the previous recurrence. A precise histological analysis after paraffin fixation was necessary. When second line surgery was indicated, patients had to go through another surgical procedure. If needed, MTM could also indicate another treatment adapted to each patient, allowing a personalized management.

We reported a high number of close margins associated with a second line treatment even if the recurrence rate remains acceptable. The use of MMS could definitely decrease the risk of insufficient margins and lower the need of a second surgery.

The recurrence rate in this study is 4.1 %. This rate can be compared with other series of patients, with up to 9.5 % [23] recurrence rate.

Recurrent BCC have a more aggressive behaviour and a higher risk of recurrence. In this study recurrent BCC had a recurrence rate of 11.5 %, which seems to be higher than with MMS. It could be another argument to indicate MMS for high-risk BCC. Primary BCC have a lower recurrence rate of 2.8 %.

It is interesting to point out that all recurrences in the study occurred with high risk subtypes. The main drawbacks of our study rely on its retrospective nature. This is mostly a descriptive article.

Although basal cell carcinomas rarely metastasize, with rates going from 0.003 % to 0,55 % [24], its local destruction potential led to the definition of locally advanced BCC, with its

own particularities and management issues and a main risk of orbital invasion. In several studies the leading cause of orbital exenteration is basal cell carcinoma, with a number of cases reaching 53 % [25]. In the study, none of the patients needed an orbital exenteration.

CONCLUSION :

A multidisciplinary management of basal cell carcinomas of the eyelid, including an initial macroscopic surgery, a histopathological analysis stating the histological type and the size of the margins, along with a discussion in a multidisciplinary team meeting about the possible indication of an additional treatment allows, in our experience, a recurrence rate of 4.1 %.

CONFLICT OF INTERESTS :

The authors declare having no conflict of interest related to this article.

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Table 1. Basal Cell Carcinoma of the Eyelid in 171 Patients : Patient Demographics, Diagnosis and Management. BCC = Basal Cell Carcinoma

Characteristics	Patients (n= 171)
Patient informations (n=171)	
Age (min-max range)	74.2 (14-94%)
Female	109 (63.7%)
Male	62 (36.3%)
History of other cancer	26 (15.2%)
History of previous BCC	38 (22.2%)
Clinical informations	
Upper eyelid	16 (9.4%)
Lower eyelid	131 (76.6%)
External canthus	4 (2.3%)
Internal canthus	12 (7.0%)
Peri Orbital	8 (4.7%)
Mean diameter (min-max)	10.2 mm (3-28)
Clinical appearance	
nodular	115 (67.3%)
Infiltrated	44 (25.7%)
Superficial	5 (2.9%)
Sclerodermiform	7 (4.1%)
Surgical management	
Time between diagnosis and surgery (min-max)	28.7 days (1-293)
Pentagonal resection	151 (88.3%)
Superficial resection	20 (11.7%)
Reconstruction procedure	

Direct stitching	62 (36.3%)	
Temporal sliding flap	89 (52.1%)	
Eyelid Reconstruction using nose cartilage strips	20 (11.7%)	
Histological data		
Nodular	76 (44.4%)	
Sclerodermiform	30 (17.5%)	
Infiltrated	55 (32.2%)	
Superficial	10 (5.9%)	
Margin analysis		
Sufficient margins	120 (70.2%)	
Close margins	13 (7.6%)	
Tumoral invasion of margin	38 (22.2%)	

Table 2. Second line management after the initial surgery (171 pts). † Insufficient margins if < 1mm for a non recurring nodular BCC, or < 2mm in every other case

	Histological margin analysis (number of patients)		
Secondary Management	Tumourous Margins (38)	Insufficient Margins† (13)	Sufficient Margins (120)
Surgery	18	1	0
Radiotherapy	9	8	0
Half-yearly Surveillance	11	4	0
Yearly Surveillance	0	0	120