CLINICAL SCIENCE

A reappraisal of cryosurgery for eyelid basal cell carcinomas

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Background/aims: Liquid nitrogen spray freezing has been successfully applied for basal cell carcinomas in the eyelid region, but is not yet in general use. The reasons for this were analysed and the development of a more reliable, safer cryosurgical technique aimed for.
Methods: New cryosurgical apparatus, contact probes with increased freezing power, and a special application technique were developed and clinically tested in a consecutive series of 221 patients with primary basal cell carcinomas of the lid region. Special efforts yielded follow up reports of 220 out of the 221 patients.
Results: Experimental measurements and clinical results demonstrated that this cryosurgical technique was at least as effective as spray freezing, with lower risks. The rate of recurrent tumours in patients followed up for 5 years or longer was 5.1% (surgeons first result) respectively 0.6% (result after optimised second cryosurgery). The figures were 6.8%, respectively max 2.7%, when including all patients, independent of follow up time.
Conclusion: Traditional surgery and histopathology, still used at numerous places, resulted in higher recurrence rates despite extended loss of healthy eyelid tissues and should be abandoned. Micrographic surgery is considered mandatory to save more of the healthy structures and to obtain lower recurrence rates. Cost and time require worldwide restriction of micrographic surgery to selected cases. Updated cryosurgery provides a low cost option to micrographic surgery and results in preservation of eyelid structures and lacrimal pathways, tarsal plate, lid margin. It provides excellent cosmetic results. Thus, primary basal cell carcinomas in the eyelid region of suitable size and location should receive updated cryosurgery, and tumours beyond its range micrographic surgery.

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Zacarian,[1] Fraunfelder,[2] and Matthäus[3] were pioneers who used liquid nitrogen spray applications very successfully to eradicate basal cell carcinomas of the eyelids. The results were not as good in the hands of other surgeons. This, the fear that liquid nitrogen leaking away could cause serious freezing effects on the eyeball, and the considerably higher income from surgical interventions hindered the spread of the method. Many ophthalmic surgeons still prefer exclusively surgical removal followed by reconstructive surgery. Micrographic surgery and histopathology can be time consuming as well as an extra expense. It is usually an inpatient procedure. I describe our long term results with an improved cryosurgical technique for the treatment of basal cell carcinomas of the eyelids and adjacent areas.

PATIENTS AND METHODS

I analysed the background of diverging results and tested the use of new, more efficient, contact cryoprobes. Cryosurgical tumour destruction depends on the freezing rate (temperature decrease per time unit), as well as ice formation and temperature level. A brass block was supplied with a thermocouple, connected to a temperature recorder. The temperature decrease during liquid nitrogen contact or spray freezing was recorded and compared. The cryosurgical apparatus (Fig 1) was used in 1979–88 at a working pressure of 2.0 bar (200 kPa) and connected to the spatula-shaped contact probe (Fig 2) by means of a flexible vacuum insulated tube. A new, smaller cryosurgical apparatus (Fig 3) and even more effective contact probes with thin walls (Fig 4) were used from 1989 to 1995 (end of study).

Starting in 1979, 221 consecutive patients with basal cell carcinomas of the lid area (primary tumours) were treated. All patients were advised to return to our outpatient department on the first and third postoperative day, and to their referring ophthalmic surgeon on the fifth or sixth day, then every 3 months for 3–5 years (depending on tumour type) to us or to him. The evaluation of the long term results was based on the files of our hospital, reports of the referring surgeons, and reports of the patients.

To get as many long term results as possible I located patients who had moved and changed their doctors with the help of their relatives, former neighbours, nearby drugstores, or municipality registration offices. The study was supervised by Professor W Leydhecker, head of the University Eye Hospital Wuerzburg.

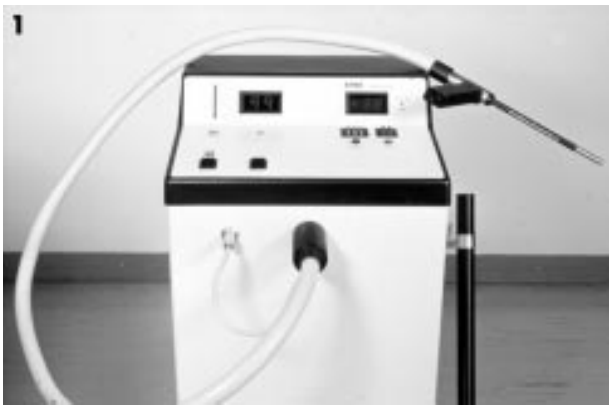

Figure 1 Cryosurgical equipment Erbokryo PS (made by Erbe Elektromedizin GmbH, Tuebingen, Germany) for liquid nitrogen cryosurgery, used for treatment of the first series (1979–88). The equipment was connected to pistol handle and contact probe by a relatively thick, vacuum insulated flexible tube.

Figure 2 Spatula-shaped hollow contact probe used with the equipment of Figure 1.

Figure 3 Cryosurgical equipment Erbocryo SN, used for treatment of second series (1989–1995). Pistol handle and contact probe are connected to the equipment by a much thinner, more flexible vacuum insulated tube. Working pressure used: 2.0 bar (200 kPa). Future equipment will be smaller, consisting of a 1 litre container and a separate storage vessel. (From Buschmann,[31] courtesy of Enke/ Thieme publishers.)

The surgeons involved in the first series (1979–88) were eight senior staff members and seven residents (supervised). Patients in the second series (1989–95) were all treated by the same experienced surgeon.

Inclusion criteria

All patients with the clinical diagnosis of basal cell carcinoma were included (in doubt: preoperative biopsy), if they agreed to have cryosurgery instead of surgery with plastic reconstruction (informed consent). Our contact probes could provide reliable tumour destruction in more than 3 mm thickness of compressed tissue (the newer probes even more), but I considered 3 mm as the safety limit. Thus, the tumour thickness limit was 6 mm (compressed) if amenable from skin and conjunctiva surface of the lid. The contact probe was applied to the back (basis) of tumours, if not amenable from the conjunctival sac, through a tunnel incision, which in addition permitted us to take a proximal biopsy to prove that the tissue there was free of tumour cells. The lateral tumour extension was unlimited. All locations were included (lids and adjacent areas). The majority of tumours were located on the lower lid and/or medial angle, only few on the upper lid or lateral angle, as usual.

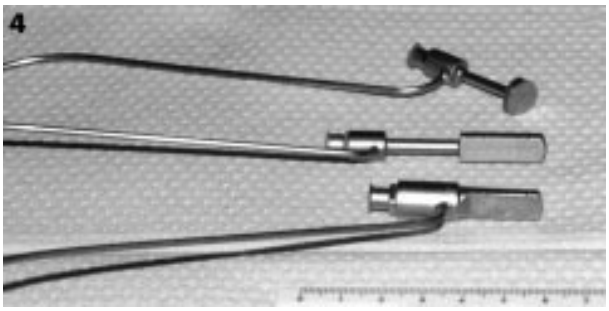

Figure 4 Contact probes used with the equipment of Figure 3. Improved construction details of the walls resulted in a marked increase of freezing efficiency.

Exclusion criteria

These were adherence of the tumour to bones or orbital fascia; morphoea type cancers, if this histopathology was detected preoperatively; suspected lymph node metastases, biopsy findings other than basal or squamous cell carcinoma.

Cryosurgical application technique

A preoperative biopsy was taken several days before cryosurgery if the clinical diagnosis was doubtful. Local infiltration anaesthesia (Mepivacaine 1% or 2 %) combined with vasoconstriction (Ornipressin) was applied. After waiting for a visible anaemia, an intraoperative biopsy was taken from the tumour centre (Elliot trephine) to obtain a histopathological diagnosis. Three cryocycles (fast freezing, slow thawing) were applied to each area of the tumour and the safety zone with the spatula contact probe firmly pressed and frozen to the wet tumour and skin surface respectively, followed by another two to three cycles with the contact probe at the conjunctiva of the lid. Tissue temperature monitoring with thermocouples and temperature recorder was performed in our early cases and in difficult ones. Each tissue part should be at –40°C (minimum) for at least 20 seconds within each cryocycle. A generous safety zone has been treated as well, because no problems of defect coverage arise or loss of lacrimal pathway function. If the lateral extension was poorly defined, an especially large safety area was treated and a biopsy taken at the lateral margin of the treated area. Excisions at the visible tumour margins plus cryosurgery for possible remnants were applied in 22 cases.

RESULTS

The analysis of the liquid nitrogen spray technique revealed that there are equipment factors and application factors which are decisive for the freezing effect on tissue. The important equipment factors are working pressure and diameter and shape of the spray tip. Application factors which can lead to incomplete tumour eradication are the tip to tissue distance, the angle of the spray to the tissue surface, the speed of spray movement across the tissue, and the distance between parallel lines of spray movement. It is difficult for the surgeon to keep all these parameters at optimum. Another source of failure was apparent lack of basic cryosurgical knowledge. Using contact probes, firmly frozen to a wet tissue surface, we could reduce the number of variables. A well defined area, corresponding to the size of the contact probe, was treated under homogeneous conditions. Overlapping application areas were used for tumours of larger extension. Formerly, the contact probes available provided much less freezing efficiency than spray application. This is why the pioneers[1–4] and others preferred the spray in the past. Our measurements have

Table 1 Cryosurgery of primary basal cell carcinomas, tumour free postoperative courses, and follow up times

1st series, cryosurgery	Follow up (mean) (years/months)	Range (years/months)	Average age at operation (years)
Number of patients			
79 (a)	12/1	8/6 to 18/0	61.7
87 (n)	6/2	0/1 to 15/1	74.2
Excision (marginal) + cryosurgery or spray			
13 (a)	11/3	8/8 to 16/2	57.4
9 (n)	5/0	0/7 to 12/9	75.2
2nd series, cryosurgery			
18 (a)	3/8	1/5 to 6/7	70.5

Patients alive at final study evaluation = a, patients not alive = n. For patients with recurrent tumours following cryosurgery of primary basal cell carcinomas see Table 2.

proved that this has changed as a consequence of the development of new cryosurgical apparatus and better contact probes. Starting with the brass block at room temperature spray freezing resulted in a faster freezing rate (temperature decrease) between 20°C and 0°C. But below 0°C, in the decisive range between 0°C and –40°C, contact freezing, using our cryosurgical apparatus and contact probes, provided the higher freezing rate (faster temperature decrease). This allowed us to start a patient series using contact freezing.

Results

The postoperative course of 220 patients with primary basal cell carcinomas was evaluated (Table 1; follow up information was not available in one patient). When I restricted the evaluation of the long term results to those 157 patients with primary basaliomas who were followed 5 years or longer I found eight recurrent tumours (5.1%). Seven of these recurrent tumours were treated again using cryosurgery, and the patients remained tumour free. The other patient (0.6%) had excisional surgery; it is not known whether a second cryosurgery could have resulted in a tumour free course in this case.

However, I evaluated, in addition, all other patients who were followed for less than 5 years (lost after some years of follow up, died from other diseases).

I found 15 recurrent tumours (Table 2) in the group of 220 primary basal cell carcinomas (6.8%). Seven of these remained tumour free following a second cryosurgery, six were not treated again this way; surgery was preferred (2.7%). This is not the final recurrence rate, because they possibly could have been treated successfully via a second (or proper primary) cryosurgery.

The recurrent tumours were all seen in the first series of patients (1979–88), and occurred mainly in patients treated in the first years of this study. The second series (1989–95) consisted of 18 primary basal cell carcinomas and six recurrent tumours, sent to me following excisional surgery (one morphoea like). All remained tumour free in the postoperative course, but the follow up time is still too short (mean 3 years 8 months, range 1 year 5 months to 6 years 7 months). An even more effective new cryosurgical unit and probes were used (Figs 3 and 4), and all of these operations were done by one experienced cryosurgeon.

Complications of cryosurgery

There is permanent loss of ciliae in the treatment area. This is unimportant on the lower lid, but troubling on the upper one. Depigmentation persisted sometimes for months. It might be troublesome in black patients (we had none). Hyperpigmentation did not play a part. The collagen fibres do remain nearly unchanged, in contrast with burns. This is why I have seen cicatricial changes of the skin in only a few patients who developed wound infections because of no topical antibiotic treatment. Surgical interventions were not needed. Shrinking of pre-existing scars (from preceding excisions), as well as entropium or ectropium, were sometimes seen following cryosurgery of recurrent tumours.

Table 2 Patients with recurrent tumours after cryosurgery, treatment results

	Age	Histopathology	Location	Biopsy	Treatment	Result	Follow up, remarks (y/m)
1	56	basal cell naevus syndrome	lower lid, lateral	before	cryosurgery	tumour free (eyelids)	11/1; annually up to 20 new tumours at the body
2	68	basal cell carcinoma	medial angle	during	cryosurgery	tumour free	14/1; 13 y ago basal cell carcinoma at temple
3	62	basal cell carcinoma	medial angle	during	cryosurgery	tumour free	10/6
4	50	basal cell carcinoma	lower lid, middle	during	cryosurgery	tumour free	8/6
5	73	morphoea-like basal cell carcinoma	medial angle	before	cryosurgery	tumour free	0/8; died from other disease
6	77	basal cell carcinoma (lid)	upper lid, middle	before	cryosurgery	tumour free (lid)	3/0; multiple morphoea like basal cell carcinoma at face
7	60	basal cell carcinoma	lower lid, middle + lateral	before	cryosurgery	tumour free	12/3
8	46	basal cell carcinoma	lower lid, medial	during	cryosurgery	tumour free	6/7; 1st operation = excision + cryosurgery
9	50	basal cell carcinoma	lower lid, middle + lateral	during	cryosurgery	tumour free	10/5; 1st operation = excision + cryosurgery
10	47	basal cell carcinoma	nasal of med angle	during	excision	tumour free	13/6
11	57	basal cell carcinoma	lower lid, medial	during	excision	tumour free	1/10; 8 years interval
12	53	basal cell carcinoma	median angle + lower lid	during	excision	tumour free	3/0; 5 y interval 2 y ago basal cell carcinoma of the temple
13	49	morphoea-like basal cell carcinoma	median angle and nose	during	excision	2nd recurrent tumour	laser surgery, 4/11, tumour free
14	67	basal cell carcinoma	lower lid, median + lateral	none	none	bad general health	died 5 m after diagnosis of recurrent tumour
15	39	(1) basal cell carcinoma (2) morphoea-like (recurrent tumour)	median angle + lower lid	before and during	cryosurgery, excisions	3 times recurrent tumour	again suspected recurrent tumour

Recurrent tumours following cryosurgery of primary basal cell carcinomas within 1st series (2nd series: no recurrent tumours). The recurrent tumours developed at the site of the primary tumour or in directly adjacent areas. Recurrent tumours following excisions and their treatment were described by Buschmann.[31]

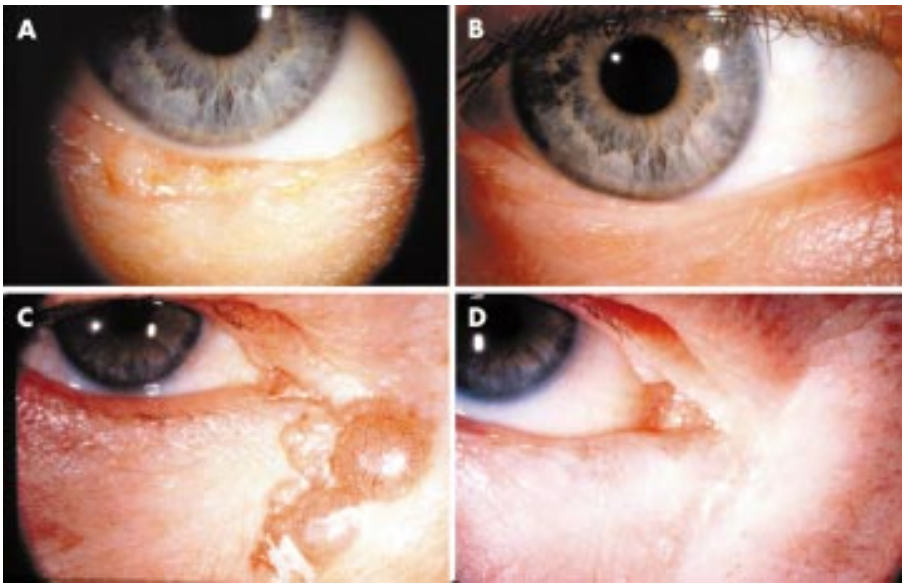

Figure 5 (A) Patient aged 33, basal cell carcinoma extending along the lid margin at nearly full length. (B) Result 3 months after cryosurgery which included the lacrimal punctum. Lacrimal pathways remained patent. Normal position and function of the lower lid. Follow up 18 years. (C) Unusual shape of a basal cell carcinoma. Patient aged 65. (D) Result 2 years 6 months after cryosurgery. Lacrimal pathways patent, follow up 12 years, 6 months. (A–C from Buschmann,[31] courtesy of Enke/Thieme publishers).

Scarring of the punctum or canaliculus occurred in a few patients in the first series in whom this area was fully involved in the treatment. Surgery for epiphora was not needed (elderly patients). Scarring was never found since we implanted a silicon canaliculus inlay for 1 week after freezing. Conjunctival overgrowth on the lid margin after spray cryosurgery has been reported.[3] I have seen it rarely, in mild form, possibly due to our application technique: treatment of the skin surface and conjunctiva gives both sides an equal chance to reach the rim. A marked transient oedema could develop, but it was much smaller since we used antioedematous drugs. It disappeared within 2–5 days. Hyperaemia lasted in some cases for months.

DISCUSSION

The precondition for efficient contact freezing was the use of a powerful cryosurgical unit (working pressure 2.0 bar, 200 kPa) together with contact probes of special design, connected by a flexible tube so that they could easily be placed upon each tumour from skin and conjunctiva surface, independent of its location.

Comparison of our treatment results with published series proved rather difficult—the inclusion/exclusion criteria (tumour size) were different, as well as the tumour locations, the follow up periods, and the number of patients with unknown course. It seems that our results are not worse (and are possibly better) than those in cryosurgical series based on spray applications (1–7.6% recurrent tumours).[4–11] The higher figures were usually related to the inclusion of larger tumours (>10 mm diameter) or recurrent tumours and a higher rate of long term controls. Contact probes with too low freezing power (equipment IKG 1) had been used in some of the early patients.[7 10] Large dermatological series of basal and squamous cell carcinomas were reported by Kuflik and Gage[12] and Graham.[13] They found 1% to 3.9% recurrent tumours.

In surgical series, Mohs's impressive results (0.6% recurrent tumours[14 15]) were based on micrographic surgery and histopathology. An essential aspect of his technique was his involvement in all phases of the procedure.[16] Micrographic surgery and frozen section control in all of 165 eyelid basal cell carcinomas[17] resulted in a recurrence rate of 2.19% (137 were followed at least 3 months, mean 29.1 months). Nearly all other authors restricted the use of micrographic surgery and intraoperative frozen section control to larger or recurrent tumours and to morphoea type lesions to reduce the time and efforts,[18–20] as Frank[17] recommended in the conclusion of his study. This, however, raised the recurrence rate to 4–5%. Improved conventional histopathological techniques have been developed as a compromise.[21–23]

Traditional excision and histopathology may result in a recurrence rate of up to 9.5% at a mean follow up of 2 years 7 months, minimum 3 months.[24] A 4 mm "safety" margin was not sufficient even in small, apparently well circumscribed basal cell epitheliomas.[25]

Low recurrence rates have been achieved in small tumours with radiotherapy as well, but multiple treatment sessions over several weeks are required. Complications are dry eye, obliteration of lacrimal pathways, and atrophic skin. Therefore, radiotherapy is generally reserved as a supplemental treatment to excisional biopsy or exenteration when there is very extensive involvement that is not amenable to dissection.[16 26 27]

Cryosurgery seems to be a simple procedure, but it isn't. My printed instructions, a review lecture and repeated discussions proved insufficient in some cases. The analysis of the cryosurgical protocols of the recurrent tumours revealed that the application instructions had not been followed carefully in these cases (for example, two cycles instead of three, or dry versus wet tissue surface). This explains why the second cryosurgery, working to rule, was successful. Thus, I had to differentiate between the recurrence rate achieved by the surgeons with the first cryosurgical intervention and the more favourable rate which resulted from proper use of the cryosurgical technique at a second approach. The histopathological type of the tumours (basal cell carcinoma, squamous cell carcinoma, or morphoea like) had no significant influence on the recurrence rate, according to our former analysis.[28]

Cryosurgeons should always keep in mind that the area of ice formation is much larger than that of tumour destruction (thermorecorder recommended). They should acquire basic knowledge of cryobiology, and pass a training programme as recommended in the guidelines of the dermatologists in the United States.[29] A surgeon unable to explain, on cryobiological grounds, why it is true that living cells (for example, sperms) can be kept alive for a long time using liquid nitrogen storage, but all tumour cells can safely be destroyed with the same

liquid nitrogen and at the same temperature, should never start cryosurgical treatment! The first treatment gives by far the best chance of success.[30]

What justifies these training efforts and the use of cryosurgery?

Cryosurgery, even if compared with micrographic surgery, preserves much more healthy eyelid structures (tarsal plate, lid margin, basal membranes of epithelium, vessel walls, lacrimal pathways). Thus, epithelium and endothelium can grow fast into the treatment area, the functional and cosmetic results are excellent and the lacrimal pathways remain patent.[31]

Neither entropium nor ectropium develop. Healthy, normal tissue returns (Fig 5). The treatment area can be extended without creating problems of defect coverage. Reconstructive surgery is unnecessary. The risks of dislocation of tumour cell nests or hidden growth beneath grafts are avoided. Anticoagulant therapy needs no interruption. There are no problems of wound healing should a second cryosurgical or surgical intervention be needed in the same area. Comparing recurrence rates, my figure for 5 years' controls (5.1%) had the calculation basis most similar to published statistics, but the follow up was much longer. I have demonstrated that a rate as low as 0.6% could be achieved. Cryosurgery is a cost saving outpatient procedure. Cryosurgery, instead of "traditional" excision, should now be preferred for treatment of basal cell and squamous cell carcinomas in the area of the eyelids. Micrographic surgery and histopathology should be used for tumours of larger thickness, tumours adherent to the periosteum or orbital septum, for morphoeas-like tumours, and for small basal cell carcinomas of the upper lid, if the gap in the row of ciliae can be closed.

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