

Effects of Urea Treatment in Combination with Curettage in Extensive Periophthalmic Malignancies

Evangelos D. Danopoulos and Iphigenia E. Danopoulou

Hellenic Anticancer Institute, Athens

Key Words. Urea treatment · Curettage · Periophthalmic malignancies

Abstract. 46 patients with 47 cancers of the eyelids and the canthi, large or very large in their great majority, were treated with local urea injections in combination with thorough curettage. In 7 of the above patients, the caruncle and the conjunctiva were also affected. This treatment was effective in 100% of our cases. The full recovery of the skin which had been destroyed by the cancer, without any remnants of scar or other disfigurement, is a very remarkable phenomenon; the functional condition of the lids remained quite normal as well. So we can affirm that in extensive periophthalmic carcinomas, in which cure with conventional methods is very difficult or almost impossible, as in some reported cases, the afore-mentioned treatment gives the most beneficial results, without any of the disadvantages of these methods.

Introduction

Our early observation that human urine has an anticancer action led us to define that it is due to urea [1]. This anticancer action of urea has been further proved by the very good results of the oral urea treatment of liver malignancies [2]; the complete cure of epibulbar malignancies untreatable with the conventional methods [3]; the cure of inoperable advanced breast malignancies [4]; the management of advanced malignancies of the uterus cervix, the penis

and the liver by *Gandhi et al.* [5] and the eradication of well-established skin melanomas in hamsters by *Ecanow et al.* [6].

In a previous article, we described the results of urea treatment in 112 patients with malignancies localized in different areas of the skin [7]. The first group of 57 of these patients was treated with only urea injections in the healthy skin around the cancer, and the second group of 55 patients was treated by combination of urea injections with scratching off of surface of the cancers and local treatment with urea pow-

der. The difference between these two treatments was obvious, since the treatments were beneficial in 73% of the first group and in 91% of the second group.

In the period between June 1973 and June 1976, we treated 129 patients with 151 skin malignancies. 46 of these patients had 47 cancers situated on the eyelids, the canthi or both and, except 2, all of them were large or very large in size. In such cases, the conventional methods of treatment (surgery and radiotherapy) entail many complications, often resulting in cosmetic and functional disturbances and, according to *Duke-Elder and MacFaul* [8], 'wherein malignancy is high and the disease is at an advanced stage, no treatment will suffice to prevent blindness or death'.

According to the opinion of experienced surgeons, the lid tissues will stretch to allow closure of defects up to a quarter of the total length and, consequently, if more than that is missing a method of reconstruction must be applied [9, 10]. Therefore, the length of the eyelids being almost 29–30 mm, one must consider the cancers with lengths between 7 and 14 mm as large and over 15 mm as very large, because the reconstruction operations are extensive.

The primary localization of the cancer in one of the canthi or the extension to one or both of them from the eyelids makes the prognosis very serious, even if the lesions are very small. The reason is that the treatment of preference, namely surgical excision, is not possible without damage to the lacrimal drainage, the plastic operation is very difficult and recurrences are very common. This treatment is much more difficult if the close area of the eye (conjunctiva or caruncle) is affected, as it was the case in 7 of our patients. This is the reason why many

of these patients with canthus cancer sooner or later undergo enucleation of the globe or exenteration of the orbit. Therefore, the results of urea treatment in combination with curettage in case of large and very large eyelid cancers and in cancers of the canthi reported here are of particular significance.

Patients and Method

Patients

Our 46 patients were seen at the Hellenic Anti-cancer Institute 'St. Savvas', Athens, from June 1973 to June 1976. 26 of these patients were men and 20 were women. One of them had two cancer sites.

Ages ranged from 42 to 98, the average being 68.

Biopsy showed in 43 cases, basal cell carcinomas, in 1 case basosquamous cell carcinoma and in 3 cases squamous cell carcinomas.

From these 47 cancers, 14 were situated only on the eyelids, 20 only on the canthi and 13 both on the eyelids and the canthi. In 8 of these last 13 cases, the cancer was situated on the eyelid and extended to one canthus; 5 cancers were situated on the eyelid and extended to both the inner and the outer canthus.

From the 27 eyelid cancers, 24 were situated on the inferior and 3 on the superior eyelid and from 33 canthus sites 31 were on the inner canthus and 2 on the outer one.

The greatest diameters of our 27 eyelid cancers were as follows: 5–7 mm in 2 patients, between 10 and 14 mm in 3 and 15–60 mm in 22 patients. The greatest diameters of our 20 canthus cancers were, 6–7 mm in 6 of them, between 8 and 14 mm in 8 and between 15 and 20 mm in 6.

In 7 of these 46 patients, the tumor affected also the caruncle and the near area of the palpebral or epibulbar conjunctiva.

Method

We proceed with the treatment as follows. After local anesthesia with injections of 2–4 ml procaine or xylocaine solution around the tumor we thoroughly remove the neoplastic tissue. We then inject 10% urea solution in 0.9% saline sub-

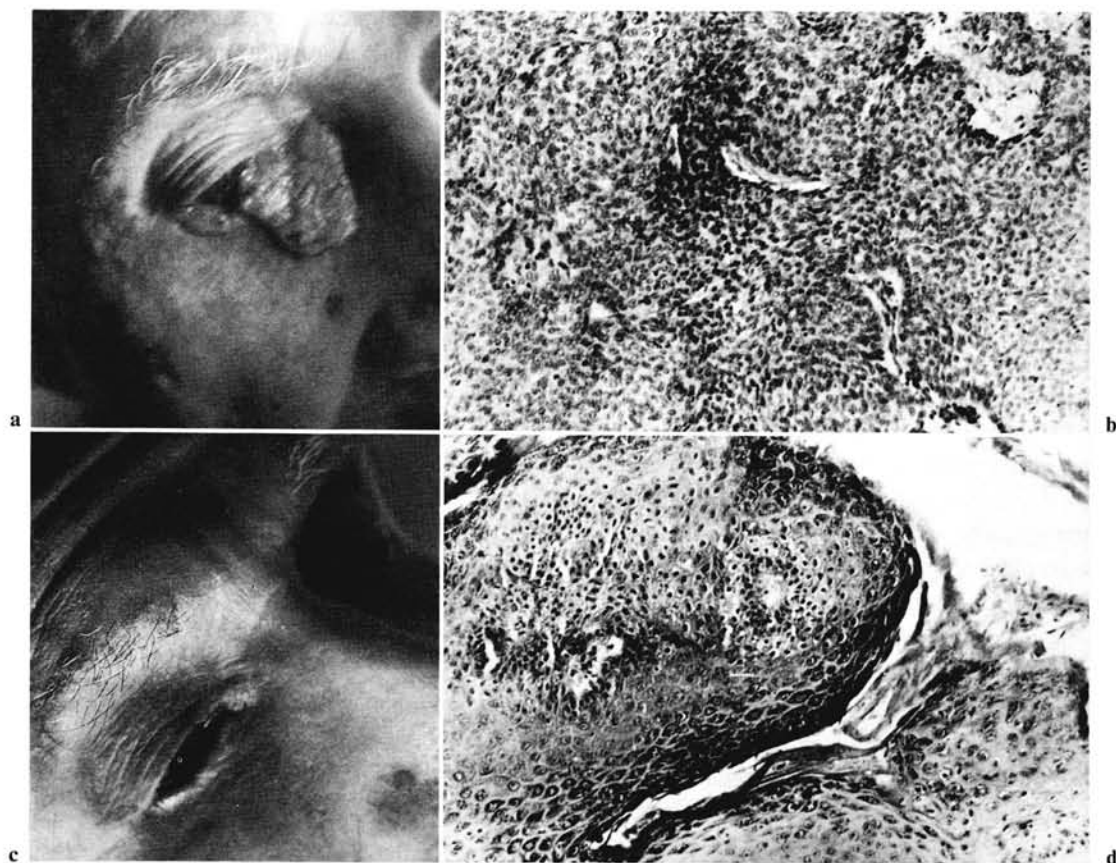


Fig. 1. Case 1. Clinical and histological findings. **a** Three quarters of the right inferior eyelid, inner canthus, caruncle and partly the cheek are affected by the cancer. **b** Histological appearance:

squamous cell carcinoma. $\times 150$. **c** Complete cure without scar after repeated scrapings and 29 urea injections. **d** Histological appearance after treatment: no cancerous elements. $\times 120$.

cutaneously and intracutaneously at a distance of about 1 cm around the lesion.¹ For large lesions, we inject of 2–4 ml of urea solution at 2–5 points around it. For smaller lesions or when the lesion has shrunk, injections at only 1 or 2 points are sufficient.

After that, we apply sterilized urea powder upon the traumatic surface (on the margins of the eyelids this, of course, is not possible) and cover

the area with a gauze dressing. The injections of urea are repeated every 2–4 days depending on the absorption of the injected urea solution. As the treatment progresses, a crust forms on the surface of the wound; we remove this crust, and if underneath there is further neoplastic growth, we excise it.

The number of therapeutic sessions ranges from 3 to 36, the average being 15.

Occasionally, despite the shrinking of the traumatic surface, the complete cure may be delayed. This can be due to deeply concealed subcutaneous neoplastic tissue between skin and tarsus in the

¹ The addition of this solution to the still unabsorbed anesthetic injected 2 min before makes it of course weaker.



Fig. 2. Case 2: Clinical and histological findings. **a** Tumorous cancer of the inferior eyelid near the inner canthus. **b** Histological appearance: basosquamous cell carcinoma. $\times 120$. **c** A photograph after curettage showing the real extension of the cancer, with remnants of it near the inner canthus. **d** Complete restoration of the eyelid after treatment. **e** Histological appearance after treatment: no cancerous elements. $\times 120$.



Fig. 3. Case 3. Clinical and histological findings. **a** Very extensive cancer occupying the upper right part of the right side of the nose, the whole inferior eyelid, the inner canthus and the inner area of the superior eyelid and the inferior half of the conjunctiva. **b** Histological appearance: spindle-

cell squamous carcinoma. $\times 120$. **c** Appearance of the lesion after 18 sessions of injections. **d** Thorough cure after treatment, with full restoration of the eyelids and the inner canthus and complete cure also of the conjunctiva. **e** Histological appearance after treatment: no cancerous elements. $\times 120$.

eyelid. Removal of this tissue by deeply introducing a small scraper and continuing urea injections bring about a rapid cure. If in spite of the apparent cure, a biopsy still shows disease, a new scraping is performed and urea injections are continued.

After the complete cure, and in order to avoid recurrences, we advise our patients to apply saturated urea solution on the treated eyelid twice daily for a period of at least 6 months. After the evaporation on the water there remains a white crust of urea upon the skin from which absorption takes place. The appliance of this solution on the canthi and the margins of the eyelids is of course impossible because urea is diluted and removed by the tears. In cases with affection of the epibulbar conjunctiva and caruncle, the treatment is completed with application of urea powder upon the conjunctiva, as described elsewhere [3].

Results

We have achieved the complete cure of all our 46 patients. This was shown not only by the disappearance of the tumor, but also by the negative findings of one or more biopsies after treatment. The regeneration of the skin in the area of the cured lesion was complete. As it can be seen from the photographs of the cases reported below (fig. 1–3), even very large cancerous lesions were cured without the least scar or disfigurement, and, therefore, without any functional disturbance. No side-effects were observed in any of our 46 treated patients.

The patients were followed up for 2–5 years and will continue to be seen for as long as possible. Recurrence has occurred in 3 of them at 1 and 4 months after the end of treatment. It must be stressed that 2 of these patients could not apply saturated urea solution on the treated area because in the one case the treated lesion was situated just on the margin of the eyelid and in the other very close to the inner canthus. The cure of

these 3 recurrences was easy with curettage and 3–8 urea injections.

Case Report

We describe 3 of the 46 treated patients with periophthalmic cancer.

Case 1

A 92-year-old man came to us in January 1974 with a cancer affecting three quarters of his right inferior eyelid, a part of the cheek, the inner canthus and the caruncle (fig. 1a). Biopsy showed squamous cell carcinoma (fig. 1b). After scraping, which was repeated three times in some areas, and 29 urea injections in the healthy skin around the lesion, the patient was completely cured without any sequelae (fig. 1c). Three new biopsies from the middle of the margin of the lid, the canthus and the conjunctiva were negative (fig. 1d). The patient is free of recurrent disease.

Case 2

A 75-year-old woman visited us in March 1974 with a protruding tumor of the right inferior eyelid, occupying seemingly one fourth of it near the inner canthus, which was also affected (fig. 2a). Biopsy showed a basosquamous cell carcinoma (fig. 2b). Nevertheless, it was shown during curettage that the neoplasm extended till the outer canthus, and the whole area of the eyelid was affected. This can be seen in figure 2c which still shows remnants of the tumor in the inner canthus before they were completely removed. After 17 urea injections along the healthy skin near the wound, the lid was almost cured, except for a small area near the inner canthus. Nine further injections did not change the situation. Then we inserted a small scraper in this area between the regenerated skin and the tarsus and we scraped out neoplastic tissue remaining deeply in the basis of the eyelid. After 7 further urea injections, the patient was completely cured (fig. 2d) and a new biopsy was negative (fig. 2e).

Due to the extension of the lesion in this case, the regeneration of the whole eyelid skin without any scar is remarkable. It is also to be noted here, how easy it is sometimes to commit errors in the estimation of the extension of the tumor before curettage.

Case 3

A 75-year-old man visited us in October 1975 with a very large ulcer, occupying an area of 60 × 35 mm and extending from the upper right side of the nose till the outer canthus. The inferior eyelid was totally destroyed and the inferior half of the epibulbar conjunctiva was edematous and red. The inner part of the margin of the superior eyelid was also affected (fig. 3a). Biopsy showed spindle-cell squamous carcinoma (fig. 3b). We began treatment with a superficial scraping and 4–6 injections around the vast area of the lesion in the healthy skin every 2–3 days. After 18 sessions of treatment, the regeneration of the lid and the confinement of the lesion in the area of the nose became quite obvious (fig. 3c). Nevertheless, the edema of the conjunctiva increased. After an incision, we found cancerous tissue under the conjunctiva and removed it. The histological findings were the same. Then we treated the conjunctiva with urea powder every 2nd or 3rd day and we continued to inject urea around the lesion. Every day, we changed the gauze dressing. After 25 sessions of injections over a period of 4 months, with an interruption of 23 days, the patient was completely cured (fig. 3d) and three biopsies from different areas were negative (fig. 3e).

Discussion

Generally, for the treatment of skin cancers, surgery and radiotherapy (the so-called conventional methods) can be used with about equally good results. But, particularly in treating eyelid and canthi cancers, one must consider not only the complete cure, but also the possible serious damage to the eyeball, the undesirable effects and the cosmetic and functional consequences of the treatment. For small cancers of the eyelids, there is no problem, but in cases of extensive cancers one has to choose between plastic surgery and radiotherapy.

Using radiotherapy, it is in the opinion of Stallard [11] 'impossible to achieve adequate protection of the lens against irradiation

by a lead contact mould set in the conjunctival sac, because rays fired either obliquely or transversely at a neoplasm involving a canthus will outflank such a protective device. The destruction of the neoplasm by irradiation is often a matter of doubt'.

Abraham *et al.* [12] reviewed 116 patients with basal cell cancers of the medial canthal region, most of which measured less than 10 mm and the largest only 17 mm. The cancers treated with radiotherapy had 20% complications (cataract, perforation of the globe, epiphora, telangiectasia, skin atrophy, conjunctival keratinisation) and 10% recurrences and those treated by surgery had 5.9% complications and 7.4% recurrences. In another paper by Swierzowa *et al.* [13], referring to the radiotherapy of 270 patients with cancer of the eyelids 'in 27% radiation induced lesions of the protective apparatus of the eye and in 5% visual impairment or loss of vision'. Fitzpatrick *et al.* [14] reported 63 complications in a total of 477 cases (13%). Lederman [15] reported a complication rate of 10% and Halnan and Britten [16] noted major complications in 40% of cases. Furthermore, Hirshowitz and Mahler [17] and Rank [18] noted that recurrences appear more frequently after radiotherapy than after surgery. A statistic from the Hellenic Anticancer Institute [1973; 19] gives the following results from radiotherapy: failures in small cancers 8%, in large cancers 36% and in very large cancers 53%. In all the treated patients with large and very large cancers a cataract was observed after radiation.

According to another statistic from the same Institute [1972; 20], a study of 131 patients who had exenteration of the orbit in a period of 22 years between 1948 and 1968

showed that 44 of those patients had a canthus and 52 an eyelid cancer. 48 out of those 96 cases had been previously treated either by radiotherapy (21 of them) or by both surgery and radiotherapy.

On the other hand, *Duke-Elder and MacFaul* [8] state that 'surgical treatment is not always entirely free from complications which, apart from continued growth of the tumour due to incomplete excision, may include epiphora, ectropion and irregularity of the lid margin'. For this reason, attempts have been made to improve the classical operation of Mustardé, and auricular skin cartilage plasty has been applied for tumors of the lid margins [9, 21].

According to *Payne et al.* [22], complications were observed in 18% of the cases treated surgically, recurrences in 12% and mortality in 2%. *Bedford* [23] observed also recurrences in 14% of his patients. According to *Stallard* [11], recurrences are rare after adequate surgery, and *Zaikowa et al.* [24] state they had no recurrences in 44 cases of malignant tumors of the lids after plastic surgery. However, the striking deformation of the face after some of these extensive operations and the functional disturbances of the artificially made eyelid makes this operation undesirable.

Besides, the great plastic operations cannot be used in cases where one or both of the canthi and much less if the caruncle and the epibulbar conjunctiva are affected. Furthermore, it is also worthwhile to mention, that very old and weak patients could not always sustain such an extensive operation as that of *Mustardé* [10].

On the contrary, urea treatment combined with thorough curettage and scrapings does not have any side-effect, it is completely nontoxic and gives the best results without

any failures. Should a recurrence take place, a short further treatment is quite effective.

Furthermore, this method is valuable because, as we showed in another article of ours, conjunctiva malignancies can be treated as easily and simply by applying urea powder on the conjunctiva and, therefore, in cases where the cancer has affected it, a combination can be used for both the skin and the conjunctiva, or the caruncle [4].

The regeneration of the skin without any scar and any disfigurement is very striking, as one can judge from the pictures of the reported cases. Sometimes, although there is full regeneration of the skin with a quite normal appearance, some cancerous elements still remain. Then further treatment is, of course, necessary.

As it has been mentioned in the Introduction, the beneficial results in a group of patients with skin cancers given only urea injections were 73%. In a second group we combined this treatment with curettage as others do it with radiation or with electrocoagulation. The improvement of our results was then striking (91%), as was described in our previous article [7]. For this reason, we did not repeat any comparative studies to be referred here.

The reason for the much better results described here must be due to the experience we have gained in the use of our method and particularly in the thorough removal of the cancerous tissue which sometimes extends very deeply under the skin.

The mechanism of the anticancer action of urea is not yet clear. According to the observations and the theory of *Ecanow et al.* [6] it is due to its destructive action upon the specific matrix of the neoplastic cells, consisting of electrolytes and water, when given in great quantities.

Nevertheless, this theory cannot explain the very good results obtained in the treatment of liver malignancies with relatively small doses of urea (10–15 g orally, daily) or the possibility of complete cure of skin cancers with only injections into the healthy skin around the cancer of a 10% urea solution. Neither is it possible with this theory to explain the complete scarless regeneration of the skin at the site of the cured carcinoma.

In our opinion, during the normal continuous destruction and regeneration of the cells, urea plays a significant role as a factor (perhaps cofactor) in the normal differentiation of the regeneration cells, which is defective in case of malignancies.

However, we cannot exclude a direct influence of urea upon the neoplastic cells; this is now under investigation.

Conclusion

Summarizing our experience we can say that:

(a) Urea treatment in combination with curettage in periophthalmic cancers was effective in 100% of our 47 cases.

(b) It is quite nontoxic and can be repeated in cases of recurrences, with the same good results, in opposition to the conventional methods.

(c) The full recovery of the skin destroyed by the cancer is a very remarkable phenomenon.

(d) In cases of extensive periophthalmic carcinomas, when a complete cure with conventional methods is very difficult if not impossible (see reported cases 2 and 3), urea treatment gives the most beneficial results.

(e) In cases of tumor of the canthi, in which the caruncle and epibulbar conjunctiva

are affected when treated with the conventional methods and exenteration of the orbit is often inevitable, urea treatment gives the best results.

(f) The treatment is simple, inexpensive, does not require any special equipment and experience in its use is quickly obtained.

Résumé

46 patients souffrant de 47 cancers – pour la plupart étendus ou très étendus – des paupières ou des commissures ont été traités par injections locales d'urée associées à un curettage très soigneux. Chez 7 patients, la caroncule et la conjonctive étaient également atteintes. Ce traitement s'est avéré efficace dans 100% de nos cas. La reconstruction totale de la peau détruite par le cancer, sans cicatrice ni défiguration est un phénomène remarquable; la fonction palpébrale est restée tout à fait normale. Nous pouvons ainsi affirmer que dans les carcinomes périophthalmiques étendus dont la guérison par les méthodes conventionnelles est très difficile, voire impossible, comme dans quelques uns de nos cas, le traitement décrit donne des résultats très satisfaisants et ne présente aucun des inconvénients de ces méthodes.

Zusammenfassung

46 Patienten mit 47 überwiegend grossen und sehr grossen Karzinomen im Bereich der Lider und der Lidkanten wurden mit lokalen Harnstoffinjektionen in Verbindung mit einer gründlichen Kürettage behandelt. Bei 7 dieser Patienten waren sowohl die Karunkel als auch die Konjunktiva betroffen.

Bei 100% unserer Fälle war die Behandlung erfolgreich. Die vollständige Wiedererholung der durch das Karzinom zerstörten Haut ohne bleibende Narbenbildung oder andere Veränderungen scheint ein sehr bemerkenswertes Phänomen zu sein. Ebenso blieben die funktionellen Verhältnisse ihrer Lider völlig normal.

So können wir feststellen, dass bei ausgedehnten periorbitalen Karzinomen, bei denen eine Behandlung mit konventionellen Methoden schwierig oder

fast unmöglich ist – wie es in einigen Fällen berichtet wurde –, die oben angeführte Behandlung zu sehr befriedigenden Resultaten führt ohne Auftreten der Nachteile, die von den anderen Methoden bekannt sind.

References

- 1 Danopoulos, E. D.: The first results of a new non-toxic chemotherapy of cancer. (Engl. summary.) *Archs Hellenic Anticancer Inst.* 6: 174–195 (1970).
- 2 Danopoulos, E. D. and Danopoulou, I. E.: The results of urea treatment in liver malignancies. *Clin. Oncol. I*: 341–350 (1975).
- 3 Danopoulos, E. D.; Chilaris, G. A.; Danopoulou, I. E., and Liaricos, S. B.: Urea in the treatment of epibulbar malignancies. *Br. J. Ophthal.* 59: 282–287 (1975).
- 4 Danopoulos, E. D. and Danopoulou, I. E.: The prospect of urea treatment in advanced breast cancers (a preliminary report). *Proc. Int. Meet. on Breast Cancer*, Athens 1978 (in press).
- 5 Gandhi, G. M.; Anasuya, S. R.; Kwathekar, P.; Bhaskarmall, and Krisnamurthy, K. R.: Urea management of advanced malignancies (preliminary report). *J. surg. Oncol.* 9: 139–146 (1977).
- 6 Ecanow, B.; Gold, B. H., and McCreery, J. W.: Tumour matrix destruction by the use of hydrophobic bond breakers: a preliminary report. *Clin. Oncol.* 3: 1–2 (1977).
- 7 Danopoulos, E. D. and Danopoulou, I. E.: Urea treatment of skin malignancies. *Lancet i*: 115–118 (1974).
- 8 Duke-Elder, S. and MacFaul, P. A.: The eyelid tumours; in Duke-Elder, *System of ophthalmology*, vol. XIII, pp. 436; 441–442 (Kimpton, London 1974).
- 9 Frueh, B. R.: A method for reconstruction of the lower eyelid. *Am. J. Ophthal.* 75: 710–712 (1973).
- 10 Mustardé, J. C.: Repair and reconstruction in the orbital region, pp. 125–126 (Williams & Wilkins, Baltimore 1966).
- 11 Stallard, H. B.: Eye surgery; 4th ed., pp. 239–240 (Williams & Wilkins, Baltimore 1965).
- 12 Abraham, J. C.; Jabaley, M. E., and Hoopes, J. E.: Basal cell carcinoma of the medial canthal region. *Am. J. Surg.* 126: 429–495 (1973).
- 13 Swierzowa, J.; Kujawska, J., and Mazur-Sokolowska, J.: Results of radiotherapy in cancer of the eyelid skin. *Polski Przegl. Radiol. Med. nukl.* 36: 521–526 (1972).
- 14 Fitzpatrick, P. J.; Jamieson, D. M.; Thompson, G. A., and Alt, W. E. C.: Tumors of the eyelids and their treatment by radiotherapy. *Radiology* 104: 661–665 (1972).
- 15 Lederman, M.: Tumors of the conjunctiva and eyelid (discussion); in Boniuk, *Ocular and adnexal tumors. New and controversial aspects*, pp. 104–109; 118–119 (Mosby, St. Louis 1964).
- 16 Halman, K. E. and Britten, M. J. A.: Late functional and cosmetic results of treatment of eyelid tumors. *Br. J. Ophthal.* 52: 43–54 (1968).
- 17 Hirshowitz, B. and Mahler, D.: Incurable recurrences of basal cell carcinoma of the mid-face following radiation therapy. *Br. J. plast. Surg.* 24: 205–211 (1971).
- 18 Rank, B.: Surgery and skin cancer. *Ann. R. Coll. Surg.* 52: 148–164 (1973).
- 19 Marangoudakis, S.; Kyparissiadis, I.; Valianatos, H.; Rammos, L.; Davas, L., and Psiloinis, H.: Radiation therapy in carcinomas of the lids (Engl. summary.) *Proc. 2nd Hellenic Congr. Derm.*, Athens 1973, pp. 452–455.
- 20 Karagounis, D.: Orbital exenteration for malignant neoplasms including eyelids (Engl. summary); thesis Athens (1972).
- 21 Hanselmayer, H. und Wisiak, H. J.: Ohr-Hautknorpel-Plastik bei Lidrandtumoren. *Ophthalmologica*, Basel 165: 464–471 (1972).
- 22 Payne, J. W.; Duke, J. R., and Eifrig, D. E.: Basal cell carcinoma of the eyelids. A long-term follow-up study. *Archs Ophthal.*, Chicago 81: 553–558 (1969).
- 23 Bedford, M. A.: Management of tumors of the lids and conjunctiva. *Eye Ear Nose Throat Mon.* 52: 357–363 (1973).
- 24 Zaikowa, M. V.; Shevtsova, N. A., and Zaikova, E. V.: Outcomes of primary plastic reconstruction for tumors of the eyelids. *Oftal. Zh.* 28: 485–488 (1973); abstract in *Excerpta med. Cancer* 28: 360 (1975).

Received: April 6, 1979

Accepted: April 10, 1979

Prof. E. D. Danopoulos
Rigillis 26
Athens 138 (Greece)