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Immediate and late treatment outcomes of radiation therapy plus cryosurgery for the treatment of conjunctival melanoma

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Purpose. *To assess immediate and late treatment outcomes of radiation therapy (RT) plus cryosurgery for the treatment of conjunctival melanoma (CM).*

Material and Methods*: The study sample consisted of 88 patients who underwent RT plus cryosurgery for the treatment of CM at SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine" during 2004-2024. Of these CM patients, 45 (52.1%) were males (age range, 20 to 88 years; median, 54.1 years), and 43 (47.9%) were females (age range, 26 to 87 years; median, 56.6 years).*

Results: *After RT plus cryosurgery, complete tumor resorption was seen in 77 patients (87.5%), and partial tumor resorption in 11 patients (12.5%). At 3 to 6 months, additional cryodestruction was performed in 8 patients (9.1%) with partial tumor resorption, which resulted in complete tumor resorption. Therefore, local control was attained in 85 patients (96.6%) after RT plus cryosurgery. Tumor recurrence was observed in 12.5% of patients, appeared as a nodule within the site of the primary tumor, and was successfully cured with cryodestruction. After RT plus cryosurgery, patients were followed up for 1 to 7 years (median, 5.1 years). Regional lymph node metastasis developed after treatment for CM in 8 patients (9.1%). Two patients developed distant metastasis. One of them developed metastasis in the lung five years post-treatment and another in the brain three years post-treatment, and tumor resorption was observed at the initial site of CM in both patients. Persistent tumor ingrowth in the orbit necessitated orbital exenteration in 3 patients (3.4%) with iatrogenic tumor.*

Conclusion: *RT plus cryosurgery is an effective method of treatment for CM with an efficacy of treatment up to 96.6% and a recurrence rate of 12.5%. The method extends opportunities for organ-preserving treatment for CM and enables retreatment in case of tumor recurrence, with rather good functional and esthetic outcomes and improved patient's quality of life.*

Key words:

ocular oncology, conjunctival tumor, radiation therapy, cryodestruction, radiation therapy plus cryosurgery, conjunctiva

Introduction

Conjunctival melanoma (CM) is an aggressive and invasive ocular tumor originating from melanocytes in the basal conjunctival layer, and accounting for 2% of all ocular malignancies [1]. The incidence of CM in Caucasian populations is 0.2-0.8 per million and is rising steadily each year [2-4].

This malignancy arises from a pre-existing nevus (7%), primary acquired melanosis (PAM) (74%), or de novo without pre-existing condition (19%). Others, however, have reported that CM originates de novo in about 5 percent of all cases [4, 5].

Kenawy and colleagues reported the rates of recurrence that were only 1.5% at a median of 2.2 years for patients treated primarily at their center and 1.9% at a median of 1.6 years for salvage therapy for patients who initially had surgery elsewhere. Other researchers reported that tumor recurrence was seen in 3-17% of patients treated for CM. In rare cases, CM may extend directly into the globe; this occurs most commonly after inadequate treatment. Orbital, nasolacrimal or sinusal invasion is also possible [6-8].

The tumors growing beyond the limbus (especially those at the plica, caruncle and conjunctival fornix) have a significantly poorer prognosis than limbal tumors. The literature reports that after treatment of invasive CM more than 50% of patients develop local tumor recurrence [9-11].

CM is a potentially lethal ocular malignancy with an overall 10 year mortality as high as 26-30% [1]. The mortality in the group of patients who had CM with PAM in which the lesion recurred (44.7%) was higher than in patients with other types of CM [12]. Late detection, inadequate treatment and the very nature of the disease may result in functional loss, loss of the globe and not uncommonly, in death [13].

The tumor may metastasize to the regional lymph nodes and distantly to the brain, lung, and liver. There is still no effective treatment for metastatic CM [1, 10, 11].

Radiation therapy (RT) is the most common component of treatment for malignant tumors, and substantially reduces the biological potential of the tumor at the expense of death of anaplastic, well-oxygenated and the most radiosensitive tumor cells. RT can change the tumor (T) status of the disease through a reduction in tumor volume and tumor invasion. These tumor regression and reduction in T

stage compared to preoperative status have been used for assessing tumor response to treatment. Tumor size reduction during RT is considered a sign of tumor radiosensitivity and an important prognostic factor [12, 14-17].

To the best of my knowledge, no study has previously reported on the use of a reduced dose of RT followed by cryodestruction for malignant conjunctival tumors. Therefore, research aimed at developing optimal reduced total boost doses of RT and methodology for cryodestruction following RT is deemed to be important. It is required to elaborate optimal reduced doses of RT and the sequence of impacts of treatment factors, and to substantiate and assess the efficacy of combination treatment with reduced-dose RT plus cryodestruction in the treatment of CM.

Cryodestruction is an effective method of treatment for CM with low rates of tumor recurrence [18-20]. It has been successfully used both as a stand-alone treatment and in conjunction with other techniques [16-20].

Therefore, in the opinion of a majority of ocular oncologists dealing with the treatment of the malignancies of the conjunctiva, although the tumors located therein can be easily approached, surgical excision with the "no touch surgery" for prevention of seeding and subsequent defect closure may be challenging. Tumor recurrence may not always be prevented with adjunct topical chemotherapy (mitomycin C, 5-fluorouracil, or interferon), ethanol, double cryotherapy, or brachytherapy. Multiple recurrences, especially those involving the orbit, necessitate orbital exenteration [20]. In the opinion of the leading ocular oncologists, there is no standard treatment for CM. The development of new organ-saving techniques for the treatment of CM is still an important task for ocular oncologists [20].

The **purpose** of this study was to assess immediate and late treatment outcomes of RT plus cryosurgery for the treatment of CM.

Material and Methods

The study sample consisted of 88 patients who underwent RT plus cryosurgery for the treatment of CM at SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine" during 2004-2024. Of these CM patients, 45 (52.1%) were males (age range, 20 to 88 years; median, 54.1 years), and 43 (47.9%) were females (age range, 26 to 87 years; median, 56.6 years). Primary tumors were seen in 77 CM patients (87.5%), and iatrogenic tumors, in 11 CM patients (12.5%). Melanoma arose de novo in 44 patients (50%), from a pre-existing nevus in 31 patients (35.2%), and from PAM in 13 patients (14.8%).

Histomorphological studies of diagnostic biopsies were performed at the pathomorphology laboratory of the institute.

A microcryogenic cylinder-and-throttle system capable of producing low temperatures within the range of -120…-90 °C depending on gas pressure in the cylinder was used to perform the destruction. The duration of cryogenic exposure depended on the amount and location of tumor tissue, dimensions of cryogenic tip, and cryogen pressure, and was determined by the use of specially designed nomograms. RT consisted of brachytherapy with a strontium-90/yttrium-90 (90Sr/90Y) beta-radiation source, a single local dose of 40 Gy and a mean total equivalent dose of 380 ± 54.0 Gy.

Patients were followed up every 3 months during the first year, every 6 months during the next three years, and once a year during the fifth year after RT plus cryosurgery.

An MS Access database was developed to store, organize and retrieve the data associated with the results of examination and treatment of patients with CM. Numerical parameters were entered as numerical data, and clinical characteristics as ordinal data. Mean and standard deviation (SD) were calculated for quantitative data. The statistical power was analyzed using G*Power 3.1 software (Kiel University, Kiel, Germany) [21].

This paper is part of the research project "To Examine the Pathogenetic Mechanisms of the Clinical Effect of (Response to) Combination Treatment for Medium and Large Uveal Melanomas and Malignant Lesions of the Palpebral, Plical, and Caruncular Conjunctiva" (state registration number, 01224U00149).

This study involved human subjects and followed ethical standards as outlined in the 1964 Declaration of Helsinki of the World Medical Association with its further amendments and the European Convention on Human Rights and Biomedicine, and relevant laws of Ukraine. The study was approved by the bioethics committee of SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine" (committee minutes dated April 22, 2025). Informed consent was obtained from all study subjects.

Results

After RT plus cryosurgery, complete tumor resorption was seen in 77 patients (87.5%), and partial tumor resorption in 11 patients (12.5%). Of note, new foci developed in the presence of complete tumor resorption in 3 patients (3.4%). At 3 to 6 months, additional cryodestruction was performed in 8 patients (9.1%) with partial tumor resorption, which resulted in complete tumor resorption.

Therefore, local control was attained in 85 patients (96.6 %) after RT plus cryosurgery.

Eleven patients (12.5%) developed late tumor recurrence after one course of treatment with RT plus cryosurgery.

Most recurrences occurred within the first three years post-treatment, appeared as a nodule within the site of the primary tumor and were usually successfully cured with cryodestruction. After RT plus cryosurgery, patients were followed up for 1 to 7 years (median, 5.1 years). Regional lymph node metastasis developed at 3 to 36 months (median, 13 months) in 8 patients (9.1%). The initial tumor location was the plica and caruncle in four patients and the conjunctival fornix in three of these eight patients. Patients were treated for regional lymph node metastasis at a cancer treatment facility near their place of residence.

Two patients developed distant metastasis. One of them developed metastasis in the lung five years post-treatment,

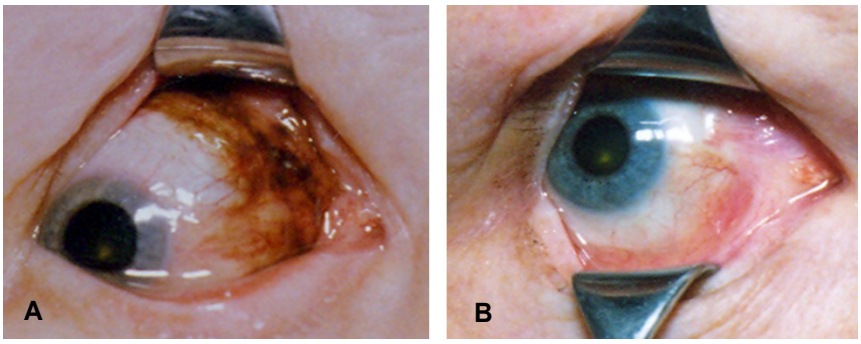

Fig. 1. Pre-malignant primary acquired melanosis of the scleral, plical and superior forniceal conjunctiva in the right eye at baseline (A) and 3 years after treatment with radiation therapy plus cryosurgery (B). Follow-up duration was 3 years.

and another in the brain three years post-treatment. Tumor resorption was observed at the initial site of CM in both patients. Interventions to address metastasis were conducted at the National Cancer Institute, Kyiv.

Persistent tumor ingrowth in the orbit necessitated orbital exenteration in 3 patients (3.4%) with iatrogenic tumors.

Iridocyclitis was an immediate complication of RT plus cryosurgery treatment for scleral CM in 3 patients (3.4%), and was promptly treated with anti-inflammatory therapy.

Scleromalacia was a late complication noted 6 months to 3 years (median, 11 months) after RT plus cryosurgery treatment for scleral CM in 6 patients (6.8%). This complication was treated with scleroplasty, which saved the affected eye in 5 patients (5.7%) and failed to save the affected eye in 1 patient; the latter patient subsequently received enucleation surgery. Persistent tumor ingrowth in the orbit necessitated orbital exenteration in 3 patients (3.4%) with iatrogenic CM.

Therefore, exenteration was successfully avoided in 96.6% of patients treated with RT plus cryosurgery for CM. Tumor recurrence was observed in 12.5% of patients, appeared as a nodule within the site of the primary tumor, and was successfully cured with cryodestruction.

Transient iridocyclitis was an immediate postoperative complication in 3 patients (3.4%) and was promptly treated with anti-inflammatory therapy. Scleromalacia was a late complication in 6 patients (6.8%). This complication was treated with scleroplasty, which saved the affected eye in 5 patients (5.7%) and failed to save the affected eye in 1 patient (1.1%); the latter patient subsequently received enucleation surgery.

The cases presented below exemplify the outcomes of the proposed RT plus cryosurgery treatment for CM.

A 52-year-old female patient (medical record no. 65432) was diagnosed with malignant PAM of the scleral, plical and superior forniceal conjunctiva in the right eye. Seven years before presentation, she had noted conjunctival pigmentation in the right eye, which was not treated before presentation. After RT plus cryosurgery, complete resorption of the lesion was observed, and no recurrence was noted over a 3-year follow up (Fig. 1).

A 55-year-old male patient (medical record no. 62511) was diagnosed with non-pigmented melanoma of the scleral and corneal conjunctiva in the left eye. She reported that she had been ill for a year but received no treatment before presentation. After RT plus cryosurgery, complete resorption of the lesion was observed, and no recurrence was noted over a 5-year follow up (Fig. 2).

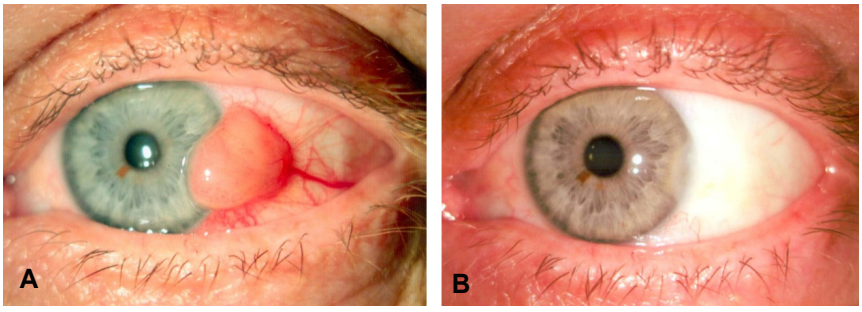

Fig. 2. Non-pigmented melanoma of the scleral and corneal conjunctiva in the left eye at baseline (A) and 5 years after treatment with radiation therapy plus cryosurgery (B). Follow-up duration was 5 years.

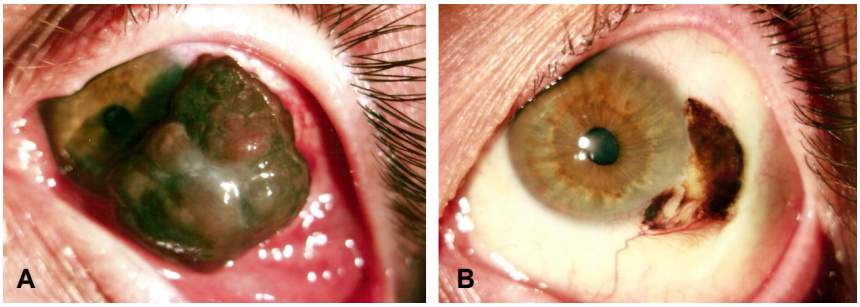

Fig. 3. Pigmented melanoma of the scleral and corneal conjunctiva (post-surgery recurrence) in the left eye at baseline (A) and 7 years after treatment with radiation therapy plus cryosurgery (B). Follow-up duration was 7 years.

A 63-year-old female patient (medical record no. 617433) was diagnosed with pigmented melanoma of the scleral and corneal conjunctiva (post-surgery recurrence) in the left eye. She had been ill for about two years. A year before presentation she underwent surgical excision of the scleral conjunctival tumor at a cancer treatment facility near her place of residence, but a recurrence occurred 6 months postoperatively. After RT plus cryosurgery, complete resorption of the lesion was observed, and no recurrence was noted over a 7-year follow up (Fig. 3).

Discussion

Conjunctival melanoma (CM) is a rare ocular malignancy. There is no standard treatment for CM and management varies between eye cancer centers [22-25].

We have proposed a method of CM treatment involving RT plus cryosurgery, which was used in 88 patients with CM. The efficacy of CM treatment using RT plus cryosurgery was 96.6%, which is in agreement with the reports on CM treatment using other methods (surgical excision with adjuvant cryotherapy, local chemotherapy (mitomycin C, 5-fluorouracil, or alpha-2b-interferon), RT (brachytherapy, proton or photon beam therapy)) [1, 22-25].

Recurrence rate is a common outcome measure in cancer surgery. In the current study, tumor recurrence was observed in 12.5% of patients after CM treatment using RT plus cryosurgery. Such recurrences appeared as a nodule within the site of the primary tumor, and were usually cured with cryodestruction. Other researchers reported that the recurrence rate after treatment for CM ranged from 3% to 17% [2, 23-29], which is in agreement with our findings.

Of note, in the current study, after CM treatment using RT plus cryosurgery, new foci developed in the presence of complete tumor resorption in 3 patients (3.4%). Previous studies, however, have not focused on this point.

Transient iridocyclitis was an immediate postoperative complication and was promptly treated with anti-inflammatory therapy. Scleromalacia was a late complication noted in 6 patients (6.8%). This complication was treated with scleroplasty, which saved the affected eye in 5 patients (5.7%) and failed to save the affected eye in 1 patient; the latter patient subsequently received enucleation surgery. Other researchers reported on possible postoperative complications like vision loss, scarring and limbal stem cell deficiency leading to persistent defects and the need for enucleation or orbital exenteration [28, 29].

In the current study, most CM recurrences were observed for patients that received primary excision of the lesion at other treatment facilities. Treatment of these patients was rather difficult and sometimes impossible, necessitating enucleation or orbital exenteration. This is comparable with findings of other studies [1, 5, 10, 23, 28].

Additionally, in the current study, the rate of patients developing regional lymph node metastasis after treatment for CM was 9.1%, which was half less than that reported by other researchers (18.2%) [2, 27-31]. Moreover, the percentage of patients developing distant metastasis after treatment for CM was 2.2% (one patient developed metastasis in the lung, and another patient in the brain). It has been reported that metastatic disease develops in 20–30% of patients with CM [32]; therefore, our data were lower than those reported in the literature.

Summarizing the above, conjunctival melanoma is a rare ocular malignancy that is potentially dangerous for the eye and life. Developing new treatment methods for this disorder is important since currently there is no standard treatment for CM.

Conclusion

RT plus cryosurgery is an effective method of treatment for CM which improves the efficacy of treatment to 96.6% with a recurrence rate of 12.5%. The method extends opportunities for organ-preserving treatment for CM, enables retreatment in case of tumor recurrence, with rather good functional and esthetic outcomes and improved patient's quality of life.

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Disclosures

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Ethical Statement: *This study involved human subjects, was approved by the local bioethics committee, and followed ethical standards as outlined in the Declaration of Helsinki of the World Medical Association and the European Convention on Human Rights and Biomedicine, and relevant laws of Ukraine.*

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Conflict of interest: *The author states that she has no conflicts of interest that might influence her opinion on the subject matter or materials described or discussed in this manuscript.*

Ethical Approval of Studies Involving Humans*: The study was approved by the bioethics committee of SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine" (committee minutes dated April 22, 2025).*

Informed Consent: *Informed consent was obtained from all study subjects.*

Data Availability Declaration: *All the data obtained or examined during this study has been incorporated into this published article.*

Abbreviations: *CM, conjunctival melanoma, PAM, primary acquired melanosis; RT, radiation therapy*