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Simultaneous conjunctival melanomas in one eye treated with both adjuvant brachytherapy and proton beam radiotherapy

Laura D. Selby [a,*], Kent Wallner [b], Evan Hall [c], Nina Mayr [b], Alexei Chvetsov [b], Andrew W. Stacey [a]

[a] Department of Ophthalmology, University of Washington School of Medicine, 325 9th Avenue Box 359608, Seattle, WA, 98104, USA
[b] Department of Radiation Oncology, University of Washington School of Medicine, 1959 NE Pacific Street Box Number 356043, Seattle, WA, 98195, USA
[c] Division of Hematology and Oncology, University of Washington Fred Hutchinson Cancer Center, 825 Eastlake Ave. E, Seattle, WA, 98109, USA

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ABSTRACT

Purpose: We describe a rare case of two simultaneous primary conjunctival melanomas in the same eye that were treated sequentially with both plaque brachytherapy and proton beam radiotherapy following wide surgical excision.

Observations: A 66-year-old male presented with two pigmented lesions that were concerning for conjunctival melanoma. One of the lesions was on the bulbar conjunctiva near the corneal limbus, and the other in the lower fornix. The lesions were surgically removed using the "no touch" technique, and pathology confirmed invasive melanoma in two separate locations on the same eye. The two lesions were then treated separately with two different forms of adjuvant radiation therapy. The forniceal tumor was treated with proton beam radiotherapy and the limbal lesion was treated with plaque brachytherapy. 30 months after radiation therapy was completed, there were no signs of local recurrence.

Conclusions and importance: The appropriate treatment for two primary malignancies in the same eye can be determined independently and, in some cases, can involve two different forms of radiation therapy.

1. Introduction

Conjunctival melanoma (CM) is a rare ocular malignancy that accounts for approximately 2–5 % of all ocular tumors and carries a 10-year mortality rate of up to 38 %.[1,2] The reported incidence of CM ranges from 0.1 to 0.9 per 1,000,000 person-years and studies have demonstrated a steady increase in incidence over the last several decades.[2] Conjunctival melanoma may arise de novo, from conjunctival nevi, or from primary acquired melanosis (PAM). An estimated 42–75 % of conjunctival melanoma cases arise from PAM, and these lesions have a lower rate of metastasis compared to those arising de novo.[2–5]

The gold standard treatment of local CM is wide surgical excision of the lesion, but several forms of adjunctive therapy are also frequently used due to the high rate of recurrence. These adjunctive therapies include cryotherapy (traditionally applied to the surgical margins intraoperatively), topical chemotherapy (including mitomycin C and interferon alpha-2B), and radiotherapy.[6]

Multiple radiation therapy options are available for ocular melanoma, including plaque brachytherapy, external beam radiation therapy (EBRT), proton beam radiation therapy (PBRT), and stereotactic radiotherapy/radiosurgery and are variably used based on preference and institutional availability.[6–8] While eye plaque brachytherapy has been largely employed for choroidal melanoma, its use has been recently expanded to treat conjunctival melanomas, including in the adjuvant setting.[9,10]

The rate of local recurrence of conjunctival melanoma is estimated to be as high as 60 %.[1,4] The most important risk factor for recurrence is location, though other factors, like tumor thickness and diameter, have also been predictive of recurrence and metastasis.[4,5] Wide local excision is considered to be the mainstay of treatment, however in many cases obtaining clear surgical margins is not possible due to the tumor's depth or proximity to important ocular structures. When the margins of the pathological specimen are positive, local recurrence rates increase significantly.[11] The combination of excision with either topical chemotherapy or radiotherapy has reduced the rate of local recurrence considerably, highlighting the important role of the adjunctive therapies

* Corresponding author. Department of Ophthalmology, University of Washington School of Medicine, 325 9th Avenue, Box 359608, Seattle, WA, 98104, USA.
E-mail address: laura.selby12@gmail.com (L.D. Selby).

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listed above.[1,4]

While conjunctival melanoma usually presents with a unilateral, unifocal lesion, few cases of separate, simultaneous, multi-focal conjunctival melanomas are described in the current literature.[12] We present a case of two simultaneous primary conjunctival melanomas in the same eye. Both of these lesions could not be resected with negative margins, and both lesions required adjuvant radiation. Radiation therapy was tailored according to the location and configuration of each individual melanoma. The two melanomas required different radiation treatments, and therefore were treated sequentially with both eye plaque brachytherapy and proton beam therapy. Combining these two radiation techniques with high prescription doses in a tightly confined space with radiosensitive normal ocular structures in close vicinity, has not been done before and presents significant challenges with respect to treatment coordination, dosimetry planning and planning imaging. Approaches to CT and MR imaging with the indwelling plaque, treatment strategy and treatment planning are presented and reviewed.

2. Case presentation

A 66-year-old male presented to a local optometrist for routine examination. Several areas of pigmentation were noted incidentally on the conjunctiva of the right eye and the patient was referred for further evaluation. Upon presentation to the ocular oncology service the patient demonstrated best corrected visual acuity of 20/25 in the right eye and 20/20 in the left eye. Intraocular pressure was 16 on the right and 20 on the left. On slit lamp exam, there were several pigmented lesions noted on the right conjunctiva. The first lesion was a large, palpable mass on the inferior lateral fornix measuring approximately 10 mm in length and 1–2 mm thick (Fig. 1A). This had not been noted by the patient due to its forniceal location. The second lesion was located at the 2 o'clock corneal limbus with associated feeder vessels and growth onto the cornea (Fig. 1B). There were also three small, flat areas of pigmentation located on the temporal lower eyelid margin, the bulbar conjunctiva, and the caruncle. The fundus exam was normal in both eyes. Ultrasonography of the right eye revealed normal choroid and ciliary body underlying the areas of conjunctival pigmentation. MRI of the orbits showed a mildly T1 hyperintense mass along the inferior right eyelid abutting the inferior aspect of the right globe consistent with a forniceal lesion confined to the conjunctiva, without evidence of intraocular or orbital invasion.

The constellation of exam findings was highly concerning for conjunctival melanoma arising from primary acquired melanosis (PAM). The patient underwent surgical excision of the multiple concerning lesions using the "no touch" technique including a wide local resection of the inferior forniceal lesion along with posterior eyelid and anterior orbital resection.[13] All lesions were excised with at least 4 mm margins. After resection of the lesion at the limbus at 2 o'clock there was residual pigmentation in the sclera which could not be removed surgically. The margins of all resections were then treated intraoperatively with cryotherapy using three freeze-thaw cycles. Histologic examination of the resected lesions showed invasive melanoma in two locations. The inferior forniceal lesion was consistent with melanoma and showed involvement of the inferior surgical margin (American Joint Committee on Cancers-AJCC- 8th Edition TNM Staging system, stage pT3c).[14] Deeper sections taken at the time of the initial resection and located posterior and inferior to the initial forniceal resection showed no evidence of melanoma. Additionally, there was invasive melanoma at the 2 o'clock corneal limbus with positive deep margins (AJCC stage pT1a). The other resected lesions at the caruncle, right lower lid lateral margin, and temporal bulbar conjunctiva all showed PAM with atypia.

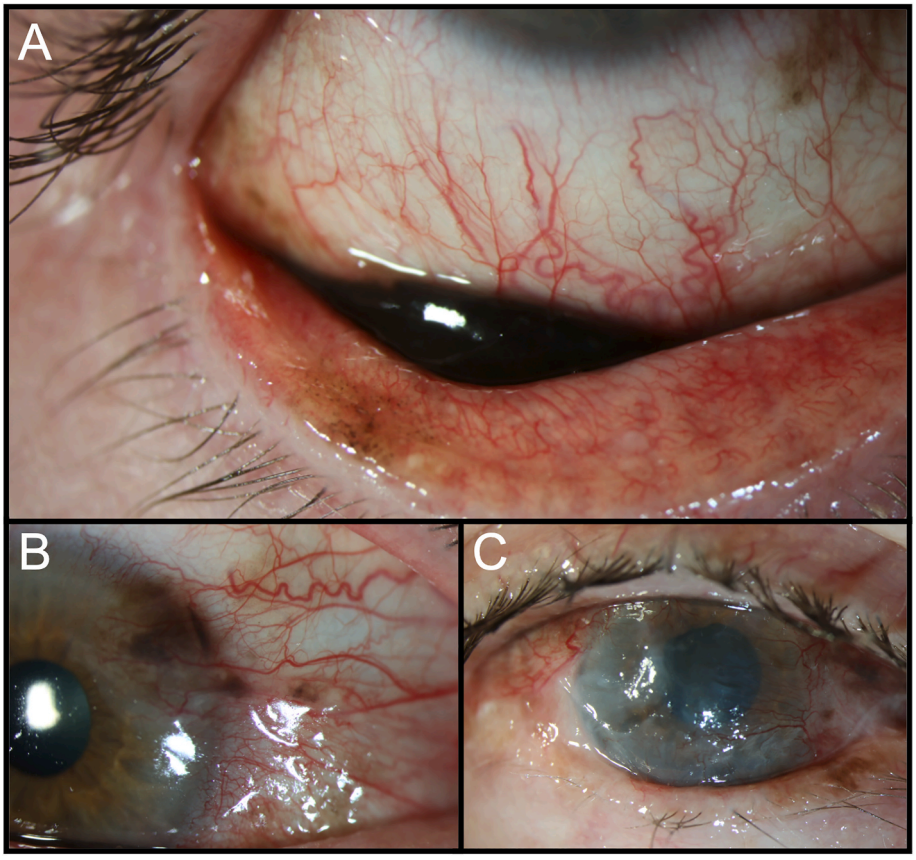

Fig. 1. Color photos of the right eye demonstrate a large, pigmented lesion in the temporal inferior fornix (A), and a flat, pigmented lesion at the 2 o'clock corneal limbus with associated feeder vessels (B). The most recent color photo of the right eye demonstrates stromal scarring and corneal neovascularization (C). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Molecular studies were negative for *BRAF* mutation. Staging computerized tomography (CT) scan of the chest, abdomen, and pelvis was negative for metastatic disease.

Because the pathologic evaluation showed deep margin involvement of the limbal lesion at 2 o'clock and suspected residual disease from the inferior forniceal lesion, it was determined that adjuvant treatment was necessary for both lesions. For the limbal lesion, no additional resection could be completed due to the intrascleral growth of the atypical cells. For the fornix lesion, while deeper sections in the orbit did not show any tumor cells, the presence of deep margin involvement in the main resected tumor raised suspicion that residual cells may still be present in the anterior orbit. Additional eye-sparing surgery was unlikely to improve local control rates in this location. Therefore, radiation treatment was required to obtain local tumor control of both tumors. The location of the two simultaneous conjunctival melanomas created a radiation dilemma. The standard treatment for scleral invasion of conjunctival melanoma in our practice is plaque brachytherapy. While this treatment would work well for the limbal melanoma at 2:00, it would not be effective for the forniceal melanoma. The fornix lesion could be targeted with proton beam radiotherapy, but in our experience and in many reports, proton beam treatment to the corneal limbus carries significant ocular surface toxicity. For these reasons, and after multidisciplinary discussion, a combined treatment with both plaque brachytherapy and proton beam radiotherapy was developed.

Radiation therapy was given in two phases, first with low-dose rate brachytherapy to the postoperative tumor bed covering the area of the corneal limbus lesion, followed by proton therapy the tumor bed in the region of the inferior forniceal lesion. For the low-dose rate brachytherapy, the postoperative bed was estimated at 7 mm diameter, and a 12 mm unnotched circular gold eye plaque developed by the Collaborative Ocular Melanoma Study (COMS) was used to cover this region with a 2 mm peripheral margin.[15] The eye plaque contained eight Iodine-125 seeds of 3.279 mCi activity each, and delivered a dose of 84.3 Gy over a dwell time of 71.8 hours to the target region (inner scleral wall). The dose was prescribed at a depth of 3 mm from the plaque surface (conjunctiva). The dose to the mid-conjunctiva was 167.1 Gy, and the dose to the contralateral sclera was 2.8 Gy.

Eight weeks after brachytherapy was completed, the patient underwent proton beam radiation therapy of the region of the resected inferior forniceal lesion utilizing unique treatment protocols developed at the University of Washington which have previously been reported.[16] While the standard treatment protocol in proton therapy for ocular melanoma is based on total dose of 50 Gy (relative biological effectiveness (RBE)) in 5 fractions, he was treated using a patient specific protocol with total dose of 48 Gy (RBE) in 20 fractions. Fig. 2 demonstrates the treatment planning for the proton beam as well as the plaque brachytherapy.

The patient was followed for 30 months after the final radiation treatment. He developed corneal limbal stem cell deficiency in the right eye approximately six months after completion of the radiation therapy. His ocular surface remained stable with moderate corneal neovascularization and some stromal scarring (Fig. 1C). His visual acuity at last follow up was hand motion in the affected eye, likely decreased due to the corneal haze and scarring. Through 30 months of follow up, there was no sign of local recurrence clinically and orbital imaging studies failed to show any sign of local recurrence. Surveillance scanning by medical oncology performed approximately 27 months after completion of radiation treatment demonstrated a new lytic lesion in the T6 vertebral body concerning for metastatic involvement. Core needle biopsy of the lesion confirmed metastatic melanoma. Molecular studies were again negative for any targetable mutations (*BRAF* or *KIT*), but they did reveal a *BRCA2* somatic mutation. The presence of a *BRCA2* germline mutation was thought to be highly unlikely since the patient had a negative family history for breast or ovarian cancer. To our knowledge, he did not undergo further germline testing.

The patient completed three cycles of palliative systemic therapy with ipilimumab and nivolumab, but subsequently developed immunotherapy-related hepatitis. Additional imaging at that time showed new liver lesions concerning for disease progression. He then began second-line therapy with pembrolizumab and lenvatinib. Shortly after initiation, the patient made the decision to transition to comfort

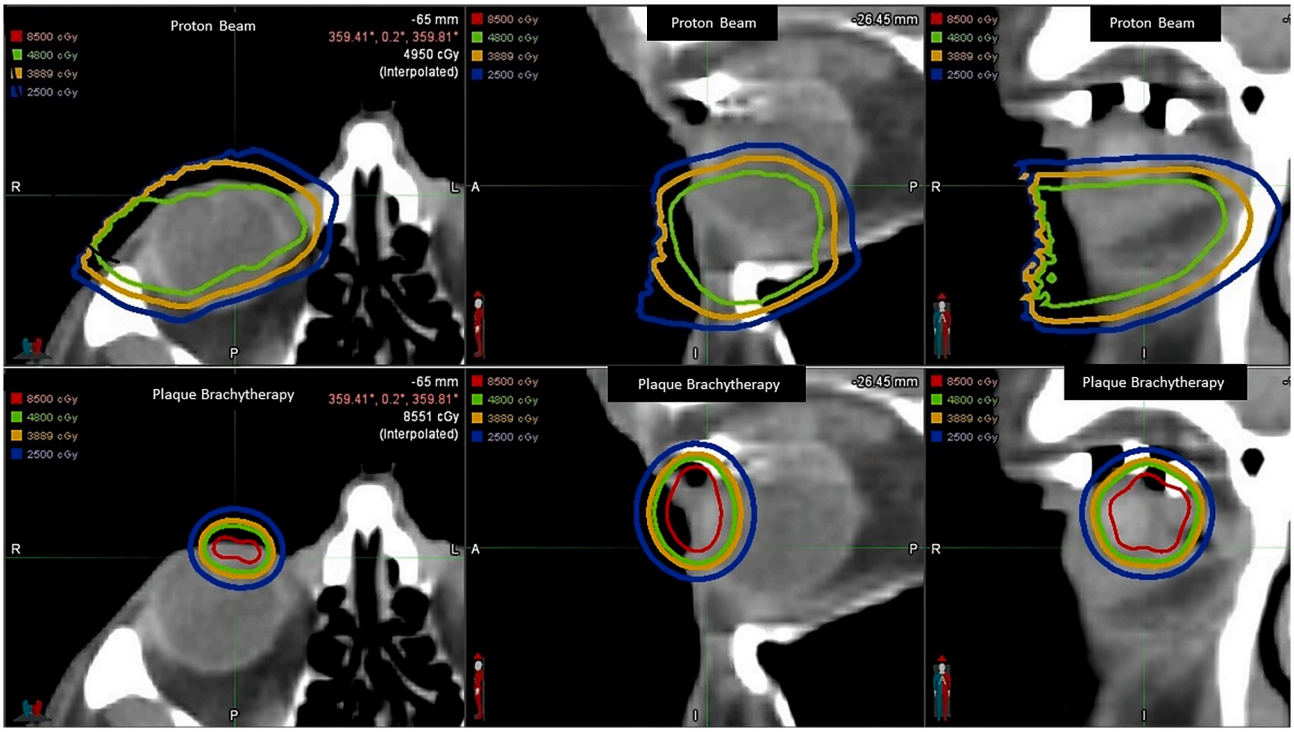

Fig. 2. Computed tomography scan of the right orbit and globe with treatment planning for the proton beam therapy and plaque brachytherapy. Isodose lines: red = 8500 cGy, green = 4800 cGy, yellow = 3889 cGy, blue = 2500 cGy. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

care and he died of metastatic disease without evidence of local recurrence 30 months after radiation therapy completion.

3. Discussion

Conjunctival melanoma is a serious, sight- and life-threatening disease that has a high rate of local recurrence. In this report, we present the case of a man with two simultaneous conjunctival melanomas each requiring separate adjuvant radiation treatment modalities to the same eye. Despite the very high risk of local recurrence in this situation, the use of combined brachytherapy and proton beam radiation has demonstrated eye salvage with 2.5 years of local tumor control.

While our patient developed distant metastatic disease several years after initial tumor resection, he maintained local control with no evidence of recurrence in the ocular structures. A possible explanation may be the presence of circulating, dormant tumor cells that later reactivate, leading to systemic failure. It is unclear how frequently CM patients without local recurrence develop distant metastasis. However, the propensity of choroidal melanomas for distant metastasis (with or without the presence of local recurrence) is well understood.[17,18] Additionally, late metastasis more than 10 years after initial resection is a well-documented occurrence in cutaneous malignant melanoma.[19]

Treatment modalities for conjunctival melanoma have advanced significantly, leading to better local control rates. Cryotherapy and a "no-touch" surgical excision technique have been shown to be important in these improvements.[1,6,13,20] In this patient, a "no-touch" technique was used for each, separate lesion resection and all surgical margins were treated with cryotherapy. However, there was still evidence of residual melanoma cells in two locations.

Each lesion in our patient had unique characteristics requiring different treatment modalities. Corneal limbus lesions are typically associated with a lower risk of recurrence and lower mortality rates, and treatment with brachytherapy in these lesions has been favorable.[9,21–23] There are several different radioactive agents used in brachytherapy, including Ruthenium-106 plaques, Iodine-125 plaques, and Strontium-90 handheld applicators. A recent retrospective analysis by Brouwer et al. found that there was no significant difference in the rate of recurrence between these agents.[22] A review of several case series evaluating the outcomes of adjuvant brachytherapy following surgical excision found that 80 % of cases experienced complete resolution of disease.[23] Brachytherapy has also been shown to significantly reduce recurrence when compared to both excision alone and excision with cryotherapy.[4,24]

Forniceal lesions are typically not accessible to brachytherapy or other forms of eye-sparing treatments and are therefore limited to forms of EBRT or exenteration as treatment options. The forniceal melanoma in our patient was large (10 mm long and 2 mm thick) and potentially deep margin-involving. For high-risk tumors (thickness greater than 2 mm, unfavorable location, multifocal lesions), PBRT and EBRT have been reported to be viable alternatives to exenteration.[23,25] Wong et al. summarized the findings in three case series and determined that approximately 85 % of cases with CMs treated with EBRT or PBRT after surgical excision showed complete resolution.[23] While PBRT allows for more precise dose delivery to cancerous lesions in comparison to other forms of radiation therapy (like EBRT), access to proton therapy is limited in many areas.[26] Unfortunately, studies have shown that there are many adverse effects associated with both EBRT and PBRT. These include dry eye, eyelash loss, cataract, and keratinization of the conjunctiva. Limbal stem cell deficiency and corneal neovascularization occur in an estimated 15–20 % of cases, and our patient developed this complication approximately 6 months after treatment with PBRT.[23,25] In our patient, who had radiation from two sources to two ocular locations, limbal stem cell deficiency was an expectation from the time of treatment planning, and the goal of treatment was globe salvage.

4. Conclusions

In a patient with multiple, simultaneous, primary conjunctival melanomas, the appropriate treatment for each lesion can be determined independently. Simultaneous conjunctival melanomas can be treated using both brachytherapy and proton beam radiotherapy. In this case, treatment tailored to the individual characteristics of each tumor led to excellent local tumor control without recurrence.

CRediT authorship contribution statement

Laura D. Selby: Writing – review & editing, Writing – original draft. **Kent Wallner:** Writing – review & editing, Writing – original draft, Resources, Methodology, Data curation, Conceptualization. **Evan Hall:** Writing – review & editing, Resources. **Nina Mayr:** Writing – review & editing, Writing – original draft, Resources, Methodology, Conceptualization. **Alexei Chvetsov:** Writing – review & editing, Writing – original draft, Resources, Methodology, Data curation, Conceptualization. **Andrew W. Stacey:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Data curation, Conceptualization.

Patient consent

The subject provided his written informed consent to publish this case. All research was conducted ethically in accordance with the Declaration of Helsinki.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Shildkrot Y, Wilson MW. Conjunctival melanoma: pitfalls and dilemmas in management. *Curr Opin Ophthalmol*. 2010;21(5):380–386. https://doi.org/10.1097/ICU.0b013e32833b7aab.
2. Kaštelan S, Gverović Antunica A, Beketić Orešković L, Salopek Rabatić J, Kasun B, Bakija I. Conjunctival melanoma - epidemiological trends and features. *Pathol Oncol Res*. 2018;24(4):787–796. https://doi.org/10.1007/s12253-018-0419-3.
3. Larsen AC. Conjunctival malignant melanoma in Denmark: epidemiology, treatment and prognosis with special emphasis on tumorigenesis and genetic profile. *Acta Ophthalmol*. 2016;94(1):1–27. https://doi.org/10.1111/aos.13100. Thesis.
4. Missotten GS, Keijser S, De Keizer RJW, De Wolff-Rouendaal D. Conjunctival melanoma in The Netherlands: a nationwide study. *Investig Ophthalmol Vis Sci*. 2005;46(1):75–82. https://doi.org/10.1167/iovs.04-0344.
5. Shields CL, Markowitz JS, Belinsky I, et al. Conjunctival melanoma: outcomes based on tumor origin in 382 consecutive cases. *Ophthalmology*. 2011;118(2):389–395.e1-2. https://doi.org/10.1016/j.ophtha.2010.06.021.
6. Vora GK, Demirci H, Marr B, Mruthyunjaya P. Advances in the management of conjunctival melanoma. *Surv Ophthalmol*. 2017;62(1):26–42. https://doi.org/10.1016/j.survophthal.2016.06.001.
7. Grimes JM, Shah NV, Samie FH, Carvajal RD, Marr BP. Conjunctival melanoma: current treatments and future options. *Am J Clin Dermatol*. 2020;21(3):371–381. https://doi.org/10.1007/s40257-019-00500-3.
8. Kosydar S, Robertson JC, Woodfin M, et al. Systematic review and meta-analysis on the use of photon-based stereotactic radiosurgery versus fractionated stereotactic radiotherapy for the treatment of uveal melanoma. *Am J Clin Oncol*. 2021;44(1):32–42. https://doi.org/10.1097/COC.0000000000000775.
9. Karim R, Conway RM. Conservative resection and adjuvant plaque brachytherapy for early-stage conjunctival melanoma. *Clin Exp Ophthalmol*. 2011;39(4):293–298. https://doi.org/10.1111/j.1442-9071.2010.02469.x.

10. Straatsma BR, Fine SL, Earle JD, Hawkins BS, Diener-West M, McLaughlin JA. Enucleation versus plaque irradiation for choroidal melanoma. *Ophthalmology*. 1988;95(7):1000–1004. https://doi.org/10.1016/s0161-6420(88)33086-1.
11. Shields CL, Shields JA, Gündüz K, et al. Conjunctival melanoma: risk factors for recurrence, exenteration, metastasis, and death in 150 consecutive patients. *Arch Ophthalmol*. 2000;118(11):1497–1507. https://doi.org/10.1001/archopht.118.11.1497. Chic Ill 1960.
12. Giblin ME, Shields JA, Shields CL, Eagle RC. Primary eyelid malignant melanoma associated with primary conjunctival malignant melanoma. *Aust N Z J Ophthalmol*. 1988;16(2):127–131. https://doi.org/10.1111/j.1442-9071.1988.tb01261.x.
13. Shields JA, Shields CL, De Potter P. Surgical management of conjunctival tumors. The 1994 lynn B. McMahan lecture. *Arch Ophthalmol*. 1997;115(6):808–815. https://doi.org/10.1001/archopht.1997.01100150810025. Chic Ill 1960.
14. Jain P, Finger PT, Damato B, et al. Multicenter, international assessment of the eighth edition of the American Joint committee on cancer cancer staging manual for conjunctival melanoma. *JAMA Ophthalmol*. 2019;137(8):905–911. https://doi.org/10.1001/jamaophthalmol.2019.1640.
15. Design and methods of a clinical trial for a rare condition: the collaborative ocular melanoma study. COMS report No. 3. *Control Clin Trials*. 1993;14(5):362–391. https://doi.org/10.1016/0197-2456(93)90052-f.
16. Lee HJ, Stacey A, Klesert TR, et al. Corneal substructure dosimetry predicts corneal toxicity in patients with uveal melanoma treated with proton beam therapy. *Int J Radiat Oncol Biol Phys*. 2019;104(2):374–382. https://doi.org/10.1016/j.ijrobp.2019.02.005.
17. Ophthalmic Oncology Task Force. Local recurrence significantly increases the risk of metastatic uveal melanoma. *Ophthalmology*. 2016;123(1):86–91. https://doi.org/10.1016/j.ophtha.2015.09.014.
18. Collaborative Ocular Melanoma Study Group. Assessment of metastatic disease status at death in 435 patients with large choroidal melanoma in the Collaborative Ocular Melanoma Study (COMS): COMS report no. 15. *Arch Ophthalmol*. 2001;119(5):670–676. https://doi.org/10.1001/archopht.119.5.670. Chic Ill 1960.
19. Friberg S, Nyström A. Cancer metastases: early dissemination and late recurrences. *Cancer Growth Metastasis*. 2015;8:43–49. https://doi.org/10.4137/CGM.S31244.
20. De Potter P, Shields CL, Shields JA, Menduke H. Clinical predictive factors for development of recurrence and metastasis in conjunctival melanoma: a review of 68 cases. *Br J Ophthalmol*. 1993;77(10):624–630. https://doi.org/10.1136/bjo.77.10.624.
21. Li Y, Fan X, Jia R. Conjunctival melanoma: update on management. *Int Ophthalmol Clin*. 2019;59(2):27–35. https://doi.org/10.1097/IIO.0000000000000264.
22. Brouwer NJ, Marinkovic M, Peters FP, et al. Management of conjunctival melanoma with local excision and adjuvant brachytherapy. *Eye Lond Engl*. 2021;35(2):490–498. https://doi.org/10.1038/s41433-020-0879-z.
23. Wong JR, Nanji AA, Galor A, Karp CL. Management of conjunctival malignant melanoma: a review and update. *Expet Rev Ophthalmol*. 2014;9(3):185–204. https://doi.org/10.1586/17469899.2014.921119.
24. Damato B, Coupland SE. An audit of conjunctival melanoma treatment in Liverpool. *Eye Lond Engl*. 2009;23(4):801–809. https://doi.org/10.1038/eye.2008.154.
25. Wuestemeyer H, Sauerwein W, Meller D, et al. Proton radiotherapy as an alternative to exenteration in the management of extended conjunctival melanoma. *Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch Klin Exp Ophthalmol*. 2006;244(4):438–446. https://doi.org/10.1007/s00417-005-0093-5.
26. Suit HD. Protons to replace photons in external beam radiation therapy? *Clin Oncol R Coll Radiol G B*. 2003;15(1):S29–S31. https://doi.org/10.1053/clon.2002.0171.