Conjunctival Melanoma in Childhood and Adolescence: A Systematic Review

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Keywords

Conjunctival melanoma · Paediatric ophthalmology ·
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Abstract

Background: Conjunctival melanoma is rare in adults and rarer in children. We systematically reviewed the presentation, diagnostic and management strategies as well as outcomes for conjunctival melanoma in children and adolescents. **Methods:** The following databases were searched: Medline, Embase, Web of Science and Scopus for cases of conjunctival melanoma occurring in children and adolescents <18 years of age. **Results:** Seventeen studies with 32 patients (18 males) were identified. The median age at presentation was 11 years (range 4–18 years). Most patients were white. Most patients presented with a conjunctival mass or naevus with a recent history of growth or change. Excision biopsy provided diagnosis and management for all cases. Adjuvant chemotherapy and radiotherapy were also used. One patient had metastatic disease at diagnosis and 3 developed metastatic disease (range 1–10 months). Two patients died from disease and one was alive with metastatic disease. Two patients had disease recurrence. Outcomes

were observed to be better where diagnosis was made earlier and “no-touch” excision biopsy was performed in an appropriate specialist setting. **Conclusions:** Conjunctival melanoma occurs rarely in children and adolescents. Surgery is the mainstay of management. The prognosis is guarded in metastatic disease due to the small sample size and limited follow-up.

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Introduction

Conjunctival melanoma is an uncommon ocular malignancy, comprising approximately 5% of all ocular melanoma [1, 2]; however, it is a matter of concern that it has increased in incidence in recent decades [3–5]. It is approximately 18–40 times less common than uveal melanoma, with an estimated incidence of 0.012–0.08 per 100,000 in adults and 0.68% of cases occur in children younger than 14 years [1]. Conjunctival melanoma is a threat to sight and life with an estimated mortality of 13–38% at 10 years in adult studies [3, 4].

Conjunctival melanoma can occur on the bulbar, forniceal or tarsal conjunctiva, as well as the caruncle [1] and

arises de novo or from pigmented lesions, such as primary acquired melanosis (PAM) or naevi [1, 2, 5]. PAM with atypia is the most important pre-malignant lesion with risk of progression to conjunctival melanoma in adults [3]. In children, the majority of PAM and naevi are thought to be benign and do not progress to melanoma [6]. In a large series ($n = 806$) of paediatric conjunctival tumours, approximately half of the cases were pigmented lesions, with naevi and PAM the majority of these, and melanoma approximately 2% of all conjunctival lesions and 3% of all melanocytic tumours [5, 7]. In this series, the authors observed that melanoma tended to occur in older children (>15 years), were thicker lesions with larger bases, had more haemorrhagic areas and fewer inclusion cysts [7].

Studies and guidelines about conjunctival melanoma focus on adults. Excision biopsy (using a “no-touch” technique) is the optimal diagnostic and therapeutic modality. Local cryotherapy or corneal epitheliectomy is performed intraoperatively where needed [2, 5, 8]. Immunohistochemical staining (S100, HMB-45, MART1, SOX10) is used to confirm diagnosis [4] as well as testing for *BRAF* mutations (an important negative prognostic factor and a target for novel tyrosine kinase inhibitors [2, 4]). However, there are no established guidelines for children, so management is extrapolated from adult data.

A retrospective analysis of conjunctival tumours seen in a tertiary ocular oncology unit found that 3% of all conjunctival melanoma occurred in patients younger than 20 years of age [7]. Optimal management of young people with this condition is therefore critical. One review summarized the paediatric (to age 15) literature from 1965 to 2006 and provided detailed information about 8 cases [1], though the prevalence of conjunctival melanoma is the greatest in older children (15–18 years) [7] so that review may be incomplete. With advances in our understanding of the biology and management of cutaneous and conjunctival melanoma in the intervening decade [5], our aim was to systematically review the literature to determine presenting features and risk factors for children and adolescents diagnosed with conjunctival melanoma and review current therapeutic modalities used and their outcomes to provide an evidence-based summary and recommendations for care.

Methods

This systematic review was prospectively registered with PROSPERO (CRD42018102779). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [9] was followed in the writing of this review.

Search Strategy

We systematically searched Medline, Embase, Web of Science and Scopus (to June 2018) to identify publications about conjunctival malignant melanoma in children and adolescents 18 years and younger. Grey literature was searched using Google Scholar. The search strategies are listed in online supplementary Appendix A (for all online suppl. material, see www.karger.com/doi/10.1159/000/497813). Reference lists of relevant manuscripts were also searched.

Inclusion Criteria

We included studies in any language of conjunctival malignant melanoma in children or adolescents that provided information about diagnosis, treatment and outcomes. Studies on benign, dysplastic or Spitz naevi (formerly known as juvenile melanoma) were excluded, as were melanoma associated with another malignancy. Where studies included people older than 18, either the majority of subjects had to be under 18 or sub-group reporting of those younger than 18 was required for inclusion.

Data Collection and Analysis

Study Selection

After removing irrelevant and duplicate studies, the abstracts of remaining articles were reviewed. Where a reference met inclusion criteria, the full text was retrieved for further analysis by 3 reviewers and was either included or excluded based on the above criteria. Discrepancies were resolved by consensus.

Data Extraction and Synthesis

The following data was extracted: patient demographics, presenting history and examination, imaging modalities used and stage at diagnosis, histopathological diagnosis, immunohistochemistry and cytogenetics, treatment modalities and their complications, follow-up duration and status at final follow-up. Given the nature of the retrieved manuscripts, meta-analysis was not performed.

Quality Analysis

As 16 of 17 included studies were case reports, a quality assessment tool was created by the authors based upon the CARE guidelines. The quality analysis of included case reports is provided in online supplementary Appendix B.

Results

Search Results

The search results and study selection are displayed in Figure 1. The initial database searches identified 733 titles. A further 6 references were added after search of the grey literature and reference lists. Fifty-four references and their abstracts were screened, with 41 full text studies reviewed. Seventeen studies remained eligible after reviewing the full-text articles with a total of 32 patients.

Included Studies

Of the 17 included studies, one was a case series of 18 patients [7] and there were 14 single case reports [2, 10–

Fig. 1. PRISMA flow diagram for study selection.

22], one publication reporting 2 cases of conjunctival melanoma [23] and one publication reporting 3 cases [6]. The case series included young adults up to 21 years of age, of whom 5 were older than 18 [7]. The median age at presentation for all cases was 11 years (range 0–18; inter-quartile range 9–14). Table 1 summarises the case reports.

Study Data

Presentation, Diagnosis and Staging

Demographics. Patients were aged between 4 and 18 years. In the case series, 33% were male and 12 of the case reports involved male patients. Where stated, there were a variety of ethnicities presenting with conjunctival melanoma, though predominately white (18 case reports, 89% of Shield's case series) [6, 7, 11, 14, 17, 21–23]. Other ethnicities included 2 Hispanic children [6, 23], African American (11% of Shields' case series) [7], one Asian Indian [10], one Turkish [16], one Asian [18].

Presentation. One patient presented with a pigmented lesion from birth. The other cases presented with either a conjunctival mass or a naevus, 10 of which had a history of lesion growth. The lesions had been noticed for some time

(1 month–14 years) prior to presentation, and 4 presented due to specific concern about increased size. Fourteen case reports involved a mass and one case reported symptoms of dry eye. Three patients had xeroderma pigmentosum. In Shields' case series, 1 patient was asymptomatic, 19 presented for investigation of a conjunctival mass or pigmented lesion and one had dry eye symptoms [7].

Examination findings varied, with a variety of sizes and macroscopic descriptions. A defined nodule or mass was found in 15 case reports and in Shields' case series, the mean melanoma thickness was 1.5 mm (range 0.3–6 mm) [7]. Pigmentation was noted in 16 case reports and 50% of the case series [7]. One melanoma was ulcerated and 6 cases reported vascularized nodules. In all cases, the diagnosis was reached after biopsy. In 7 cases, the cornea or limbus was also involved. Lesions were staged with optical coherence tomography or B-scan ultrasound of the eye in 3 cases [10, 11, 19], PET in 2 cases [10, 13], MRI brain and/or orbit in 4 [2, 13, 16, 19], CT was used in 8 cases [2, 13, 14, 18–21] 4 focusing specifically on the brain or orbits, and 4 CT neck, chest, abdomen and pelvis in the others. Other staging techniques, such as gallium bone

Table 1. Summary of case data

Author (chronological)	Year	Age	Gender	Presentation	Examination	Further Cytogenetics/ Histochemistry	Extent at diagnosis	Grade	TNM at diagnosis	Management	Outcome (duration of follow-up)
<i>Case series</i>											
Shields et al. [7] (n = 13 ≤18 years)	2017	8–18	33% M	ns	Limbal disease 56%; bulbar disease 39%; caruncle 5%; 50% temporal; 50% pigmented; mean diameter 5.8 mm; mean thickness 1.5 mm; absence of cysts 72%; feeder vessels 72%	ns	ns	ns	ns	Excision	ns
<i>Case reports</i>											
Yangzys et al. [10]	2018	16	M	Pigmented lesion OD conjunctiva since childhood, incr size in 2 years	Pigmented lesion OD conjunctiva temporal 20 × 12 mm, 2 quadrant, fornice/palp spared	HMB45+ MelanA+	Local	GX	cT1c N0M0	Excision (NTT), cryotherapy, mitomycin C	DF (9 months)
Liu et al. [11]	2017	9	F	Conjunctival mass, growing with dry eye sensation	4 × 3 mm dark pigmented lesion at temporal limbus with fine surrounding vessels	HMB45+ Ki67+	Local	G1	cT1 pT1a N0M0	Excision (NTT), cryotherapy, then re-excision with corneal epitheliectomy for positive margins, cryotherapy, and an amniotic membrane graft	DF (2.5 years)
Walters et al. [2]	2017	10	M	Pigmented lesion on caruncle since birth, growing	7–8 o'clock, 2.5 mm thick	BRAF negative	Local	G3	cT2a pT1b N0M0	Excision, re-excision (NTT), cryotherapy, amniotic membrane graft, SNLB	DF (unclear)
Salcedo-Hernandez et al. [12]	2014	16	F	ns	ns	Nil	Metastatic (nodal)	GX	pTXNIMX	Exenteration and neck dissection	Died from disease (2 months)
Al Masaoudi et al. [13]	2013	10	M	Growing OS conj naevus	ns	HMB45+	Local	G1	cT1a pT1b N1M0	Excision	Metastatic 1 month – parotid: parotidectomy, brachytherapy to conj, IFNa2b, RTx to neck and topical mitomycin C to conj, Now DF (1 year)
Burgués-Ceballos et al. [14]	2013	15	M	Conjunctival lesion since childhood with growth	11 × 9 mm temporal pigmented mass with nodular growth and basal growth	HMB45+ S100+ Melan A+ Ki67 10–25%	Local	G1	pT1bN0M0	Excision (NTT)	DF (10 months)
Cohen et al. [15]	2013	12	ns	Malignant transformation of naevus in plica	ns	Nil	Local	G1	pT1b N0M0	Excision, cryotherapy, sentinel node biopsy	DF (3 years)
Polar et al. [16]	2008	6	F	Pigmented lesion OS for 3 years, incr size 6 months. Reddish-brown	Pigmented lesion 3 × 4 mm OS temporal limbus with vascular congestion	HMB45, S100+	Local	GX	cT1aN0M0	Excision (NTT), topical mitomycin C	DF (6 months)
Brownstein et al. [23]	2006	9	F	Pigmented conjunctival lesion involving bulbar and tarsal conjunctiva, excised and recurred x2. Initial histopathology: junctional naevus	9 mm wide	Nil	Local	G3	cT2a pT1a NXM0	Excision	Recurred at ages 12, 14 and 15. Now DF (12 years)
Brownstein et al. [23]	2006	4	M	Pigmented nodule on bulbar conjunctiva, growing	Ulcerated conjunctival epithelium over nodule	Nil	Local	G3	cT1a pT1b NXM0	Excision	DF (4 years)
Akor et al. [17]	2004	14	M	Conjunctival mass	5.5 × 2.6 mm conjunctival mass with pigmentation	S-100 HMB45 positive	Local	G1	cT1a pT1a N0M0	Excision, cryotherapy, re-excision for recurrence	Local recurrence at 1 year, now DF (3 years)
Ohguro et al. [18]	2003	14	M	Pigmented bulbar mass for 2 years	Pigmented mass, round with clear margin, 4mm diameter, 0.5–0.8 mm height, prominent vessels. Temporal bulbar; Not attached to limbus	HMB45, melan A+	Local	GX	cT1aN0M0	Excision, cryotherapy	DF (unclear)
McDonnell et al. [6]	1989	12	M	Conjunctival mass since age 8	ns	Nil	Local	GX	cTXN0M0	Excision	DF (18 years)

Table 1 (continued)

Author (chronological)	Year	Age	Gender	Presentation	Examination	Further Cytogenetics/Histochemistry	Extent at diagnosis	Grade	TNM at diagnosis	Management	Outcome (duration of follow-up)
McDonnell et al. [6]	1989	12	M	Pigmented limbal mass for 3 years, growing	ns	Nil	Local	GX	cTXN0M0	Excision, re-excision for positive margins; later cyclophosphamide and dacarbazine for metastatic progression	DF (20 months)
McDonnell et al. [6]	1989	16	F	Pigmented limbal mass, biopsied, re-excised and then recurred	Temporal limbal mass OS with pigmentation	Nil	Local	GX	cTXN0M0	Excision, re-excision for positive margins. Biopsy of palpable lymph node (negative)	DF (20 months)
Mehta et al. [19]	1996	8	F	Pigmented lesion on bulbar conj 2 quarters, b/g XP	Raised, soft, smooth lesion, causing proptosis, conj diemosis, corneal involvement	Nil	Metastatic	GX	cT3c pT3c: NXM1	Exenteration	Died from disease (2 days)
Aoyagi et al. [20]	1993	10	M	Recurrent pigmented conjunctival lesion, increasing in size; b/g XP	2 × 2 mm lesion	S-100 positive, Fontana-Masson positive	Local	GX	cT1a N0M0	Excision, cryotherapy	DF (9 months)
Croxatto et al. [21]	1987	11	M	Brown lesion OS since birth, growing	Slightly elevated and pigmented lesion with engorged vessels, 3 o'clock nasal limbus	Nil	Local	G1	cT2a pT3c: N0M0	Excision; later exenteration	Disease progressed after 4 months and was metastatic at 10 months. Had exenteration and disseminated metastasis 4 months post exenteration. Alive with metastatic disease
Jensen [22]	1962	14	M	Conjunctival naevus increasing in size; xeroderma pigmentosum (XP)	10 × 10 mm lesion involving the corneal limbus	Nil	Local	GX	cT1b pT3a: NXM0	Enucleation	DF (1 year)

OD, right eye; OS, left eye; NTT, no touch technique; SLNB, sentinel lymph node biopsy; DF, disease free; ns, non significant.

scans and scintigraphy were used in 3 cases. Liu, Polat and Aoyagi [11, 16, 20] used liver ultrasound in addition to other imaging as part of a metastatic staging workup. At the time of excision biopsy, 3 patients also had sentinel node excision biopsies [2, 12, 15] and one had a fine needle aspiration biopsy of the sentinel node [6]. One patient had positive lymph nodes [12].

Where sufficient information was provided, most common clinical tumour classification (based on the American Joint Committee on Cancer TNM staging for conjunctival melanoma, 8th edition [24]) was cT1a (7 cases), with one case each cT1b and cT1c, 2 cases cT2a and one cT3c. Pathological primary tumour classification showed 3 cases pT1a, 5 pT1b, one pT3a and 2 pT3c. Two patients had reported nodal disease (N1) [12, 13] and 1 patient had metastatic disease (M1) [19].

Only one case reported *BRAF* mutation testing, which was negative [2]. No other genetic testing was reported, including for *NRAS* or *PDL-1*.

Treatment

All cases in Shields' case series were managed with excision biopsy. No chemotherapy or radiotherapy was used [7]. In the case reports, 16 were treated with excision biopsy, of whom 5 reported the use of the gold-standard "no-touch" technique for the initial excision. Five cases required re-excision, either due to positive margins or due to maximal excision of a melanoma after initial excision that did not use the "no-touch" technique [2]. Intra-operative cryotherapy was used in 6 cases. Mitomycin C was used in 3 cases [10, 13, 16] and one case also used radiotherapy for metastatic disease to the parotid gland [13]. One case used systemic chemotherapy (cyclophosphamide and dacarbazine) for metastasis to a parotid lymph node [6]. One patient had an enucleation due to continued tumour growth and corneal invasion [22] and 3 had exenterations [12, 19, 21], one due to invasion of extraorbital muscles and the lacrimal apparatus [19], one due to significant disease burden [21] and one for whom a reason was not provided [12].

Outcomes

For the case reports, 17 cases were disease free at the final follow-up, with a median follow-up duration of 1.5 years (range 6 months–18 years). Five patients had local recurrence at the same primary site (one case had 3 recurrences [23]) and 3 patients had progressive systemic metastatic disease after diagnosis – one to an ipsilateral parotid lymph node [6], one to the parotid gland and managed with parotectomy and conjunctival brachytherapy, topical mitomy-

cin C and topical interferon $\alpha 2b$ [13], and one to cervical and preauricular nodes, lung, liver and skin, with radiotherapy to the cervical lymphadenopathy [21]. Two of these cases died, one 2 days post exenteration from disseminated intravascular coagulation (cause not stated) [19] and one from progressive disease 2 months after diagnosis [12]. Shields' case series did not provide follow-up information [7].

Discussion/Conclusions

Conjunctival melanoma is rare in adults and rarer in children and adolescents. We have provided a summary of the case-based literature to date with 32 cases younger than 18 years of age reported. Most children (median age for all cases 11 years) presented with pigmented or growing conjunctival lesions and the diagnosis was reached histologically. Importantly, several cases reported the lesion was present for many years prior to assessment and it was a change in size or the nature of the lesion that prompted medical attention. Management was predominantly surgical and outcomes were generally positive, with most cases disease free at final follow-up, though the limited duration (median 1.5 years) of follow-up in this small series of case reports means this finding should be interpreted with caution. Two patients died from their melanoma. The mortality rate for conjunctival melanoma in children appears favourable compared to adults, who have an estimated mortality between 13 and 38% [3, 4]. Two case reports [6, 25] followed their patients for over 10 years. Three children had xeroderma pigmentosum [19, 20, 22], a rare genetic disorder characterized by incomplete repair of ultraviolet light-induced DNA damage with a thousand-fold increased risk of cutaneous cancer [1], comprising 10% of the total case literature.

There are no paediatric-specific guidelines for the diagnosis and management of conjunctival melanoma, so approaches suggested in the adult literature have been adapted to each case. One suggested management algorithm for adults is presented by Wong et al. [26]. All patients in case reports had excision biopsy, which serves diagnostic and therapeutic roles as histopathology is the gold standard for diagnosis [26]. A "no-touch" technique is the established method of excision [5, 27], with other intraoperative therapy such as cryotherapy or corneal epitheliectomy (used in 7 cases) when indicated by corneal involvement to cause epithelial sloughing and decrease scarring [1, 3, 28]. The "no-touch" technique, first described by Shields et al. [27] is important to minimize the possibility of iatrogenic seeding of cancer cells. Topical mitomycin C, an alkylating

agent, was used in 3 cases. While it has been shown to be useful in preventing recurrence when used as an adjunct [26], it is not recommended for primary management alone as it has poor local disease control and a high recurrence rate without surgery [4]. Topical chemotherapy is useful when excision margins have PAM with atypia, though margins positive for melanoma require re-excision [28]. One patient had an enucleation and 3 had exenterations due to extensive disease or orbital extension of the tumour. These more extensive procedures are reserved for more advanced disease or multiple recurrences, particularly in the orbit [5, 28]. Radiotherapy or plaque brachytherapy was employed in one case and has been demonstrated to be useful in adults with disease in difficult areas to operate and corneoscleral disease [29]. Radiotherapy decreases recurrence but does not confer a survival benefit in adults [8]. Its role in paediatric conjunctival melanoma is undefined, given the limited data.

Adult conjunctival melanoma is also rare, with the largest case series consisting of 382 patients in a tertiary centre and median age at diagnosis was 62 years [30]. Similar to our reviewed cases, the majority of patients were white and presented with an ocular mass. There was a greater number of patients with previous cutaneous malignancies (73 patients) and 74% of melanoma arose from PAM in this series. Only 59% of lesions were pigmented, which is similar to the Shields' paediatric case series (50% [7]) but different to the case report data, where most patients had a pigmented lesion. All patients were treated with excision biopsy. There is a high recurrence rate in the adult data, with 106 of 382 cases in Shields' melanoma series having recurrence [30], and this rate is reflected in the case report data where 5 of 14 melanoma recurred. In the adult series, 19% of cases developed metastasis and death occurred in 20 cases (5%) [30]. Though paediatric data in this review have shorter follow-up (median 18 months compared to mean 52 months in Shields' adult series), reported mortality was greater in paediatric cases (2 of 19 paediatric cases and 20 of 382 adult cases) [30]. Shields' paediatric series did not provide mortality data [7].

Pigmented conjunctival lesions should be assessed by an ocular oncologist prior to biopsy in a specialized ocular oncology centre, given the need for accurate, no-touch, excision biopsy and specialist ocular pathology evaluation. A retrospective audit conducted by an ocular oncology referral service showed that patients who had primary management in non-specialised settings had poorer outcomes in terms of disease control and survival [8]. Although conjunctival melanoma is exceedingly rare in young people [7], it is the diagnosis that must be ex-

cluded for any pigmented lesion. Several cases presented here required re-excision due to a different initial biopsy approach. Further, OCT and confocal microscopy have been suggested to improve diagnostic accuracy and aid in surgical planning [26], so it would be appropriate to recommend these as part of an oncological workup in all children with pigmented conjunctival lesions.

While the case reports detail a variety of melanoma sizes, Shields' case series found that several factors were associated with conjunctival melanoma as opposed to a benign lesion: melanoma was more common in older patients (>15 years old) and significantly more likely to be over 10 mm in diameter. With respect to macroscopic features, conjunctival melanoma was more likely to lack cysts and more likely to have haemorrhagic vessels [7].

Staging of conjunctival melanoma was also variable in our reported cases. Several studies used a combination of clinical examination and imaging, using CT, PET and/or MRI. The adult literature recommends consideration of brain imaging with MRI, abdominal imaging, particularly of the liver (via CT, ultrasound, or MRI) and chest imaging (CT), or PET-CT to provide nodal metastatic information [26, 28], though there is no clear evidence for one staging modality over another [26]. Wong et al. [26] argues this should be performed in conjunction with a medical oncologist.

Lymph node recurrence can occur more than 4 years after initial diagnosis [3] so sentinel node biopsy is indicated where a tumour demonstrates more than 2 of the following: thickness greater than 2 mm or diameter larger than 10 mm, >1 mitotic figure or ulceration seen on histopathology or non-limbal disease [31]. While PET imaging may diagnose metastatic disease, detecting microscopic disease in local lymph nodes requires sentinel node biopsy [4, 28]. Adult data estimates a 29% cumulative incidence of lymphatic metastasis in conjunctival melanoma [31]. In the reviewed case reports, 3 patients had sentinel node biopsies at presentation [2, 12, 15] and one had a fine needle aspiration biopsy [6]. One patient had positive nodal disease at diagnosis [12]. There were 3 other cases [10, 14, 23] where a melanoma met criteria that did not have sentinel node biopsies. Two patients required parotid lymph node biopsies for lymphadenopathy after initial management, with one demonstrating metastatic disease [6].

Two cases involved paediatric oncologists for follow-up and management [12, 14]. However, intended follow-up frequency and methods were inconsistent. Adult recommendations include annual ophthalmic and clinical examination, annual or biannual chest radiograph, neuroimaging (using MRI), liver function tests and possibly CT imaging

[28] as the commonest metastatic sites are the brain, liver and lungs. While X-ray and CT imaging may pose a radiation burden on the young patient, the high rate of recurrence highlights the importance of consistent long-term follow-up. This is ideally coordinated by both ophthalmologists specializing in ocular oncology and paediatric or adolescent oncologists, providing thorough, multidisciplinary, age- and development-appropriate care.

Only one case provided information on *BRAF* gene mutation testing [2]. Genetic and molecular testing are critical in the assessment of a rare malignancy like paediatric conjunctival melanoma and can aid in diagnosis, suggest targeted management and inform prognosis. Current actionable genetic alterations in melanoma include *BRAF*, *cKIT* and *NRAS*. These act upon the MAPK pathway to promote cell proliferation. Up to half of all adult conjunctival melanoma are *BRAF* mutation positive [4] and one-fifth are *NRAS* mutation positive [32]. These mutations are mutually exclusive [33]. *BRAF* mutation-positive melanoma can be managed with agents such as dabrafenib or trametinib, while *NRAS* has been targeted with binimetinib in adult cutaneous melanoma trials with limited activity [34]. Vemurafenib has been used in metastatic adult conjunctival melanoma with good response [35]. Immunotherapy with checkpoint inhibitors such as nivolumab significantly improved the overall and progression-free survival in adults with metastatic cutaneous melanoma [36] and induced complete responses in adults with metastatic conjunctival melanoma [37]. These agents have been used successfully and safely in other paediatric malignancies [38–40], though no robust data exist for children or adolescents with melanoma (conjunctival or cutaneous). A phase 1 trial of vemurafenib in paediatric cutaneous melanoma was abandoned early due to low enrolment [41].

We have provided a systematic review of published reports of paediatric conjunctival melanoma. Whereas Taban's systematic review provided information regarding 8 paediatric cases aged <15 years [1], we have expanded on this with further cases up to the age of 18 and added 6 cases younger than 15 years from after that review was published. Further, we have provided information regarding most common presenting features, histopathological and clinical staging as well as summarized the outcomes of these cases, which adds to our understanding of this rare disease. There are too few cases and no prospective trials to provide evidence for or against treatment modalities or meaningfully define a prognosis in children and adolescents with conjunctival melanoma. Follow-up durations vary between case reports and so defining clear 5- and 10-year prognostic data was not possible.

It is promising to note that the majority of cases were disease free at final reported follow-up, even where recurrent or metastatic disease was reported; however, it is acknowledged that follow-up is short. Given the fact that conjunctival melanoma is rare in children and adolescents, we propose the establishment of a prospective registry of paediatric conjunctival melanoma cases so that evidence-based guidelines can be developed, which would meet the unique medical and psychosocial needs of the young patients and their families.

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Statement of Ethics

The authors declare that they have no ethical conflicts to disclose.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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Authors Contribution

B.W.R.B.: undertook the literature searches, analysed data, wrote the first draft, ongoing manuscript revision. S.C.: analysis and interpretation of data, substantial revision of manuscript. A.M.J.: substantial contribution to interpretation and manuscript revision. M.G.: interpretation of data, manuscript revision. R.M.C.: analysis and interpretation of data, substantial manuscript revision. A.C.A.: analysis of data, substantial revisions of manuscript. All authors approved of the final version as submitted.

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