SCREENING FOR CONJUNCTIVAL MELANOMA METASTASIS

Literature review

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SAMENVATTING

Locale tumorcontrole voor het conjunctiva melanoom is de laatste tientallen jaren sterk veranderd en verbeterd. Niettemin blijft er een tumorgerelateerd overlijdenspercentage van 14% na 5 jaar tot 33% na 15 jaar. Met de invoering van het onderzoeken van de poortwachtersklier bij conjunctivale melanomen met ongunstige prognose en het screenen op locoregionale en perifere metastasen hoopt men de prognose van deze patiënten te verbeteren.

ABSTRACT

Local tumour control in conjunctival melanoma has improved in recent years. However the tumour-related death rate of these patients is still 14% at 5 years up to 33% at 15 years. With the introduction of sentinel node biopsies for conjunctival melanomas with a poor prognosis and screening for locoregional and distant metasases prognosis might be improved.

RÉSUMÉ

Le contrôle local du mélanome conjonctival a beaucoup amélioré durant les dernières décades. Néanmoins la mortalité du mélanome conjonctival due aux métastases reste de 14% à 5 ans jusqu'à 33% à 15 ans. Avec l'introduction de biopsies du ganglion sentinelle et le dépistage précoce de métastases régionales et à distance, on espère améliorer le pronostic.

MOTS-CLÉS

Mélanome conjonctival, mélanome métastasé, dépistage

KEY WORDS

Conjunctival melanoma, metastatic melanoma, screening

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received: 25.09.07
accepted: 06.11.07

INTRODUCTION

Conjunctival melanoma is a rare tumour with an incidence of 0.02 to 0.08 per 100 000 in a white population, accounting for 2 % of ocular malignancies (33, 39, 44). It represents the most common high-grade malignancy of the conjunctiva and 1 to 13% of conjunctival lesions (38, 42). Conjunctival melanoma is extremely rare in non-Caucasian populations, but it does occur (5, 42, 45). This malignancy normally occurs at 40-60 years and rarely before the age of 40 years (< 10%) (4). Conjunctival melanoma is unilateral in almost any patient described.

Conjunctival melanomas usually develop from a pre-existent lesion: a conjunctival naevus or Primary Acquired Melanosis (PAM) without or with pigmentation. In about 20% they develop de novo (7, 9, 10). As for skin melanoma, conjunctival melanoma seems to be associated with sun exposure, although they also occur at non-sun-exposed areas. It was recently demonstrated that the incidence of conjunctival melanoma is increasing (48, 55).

Local recurrence is reported in 30-50% at 5 years, depending of patient selection and local treatment (1, 7, 8, 13, 20, 30, 33, 39, 42, 43, 44, 48, 52) (table 1) [Recurrence may appear in the site of the treated primary lesion and/or elsewhere in the untreated remaining conjunctiva, most often associated with PAM]. Excision without additional treatment is associated with more local recurrences. Our group recently demonstrated that excision in combination with Strontium (*Sr90*) brachytherapy results in significantly less local recurrences, although no statistical benefit on patient life prognosis could be proven (11, 33).

Conjunctival melanomas are known to spread through the lymph system, but distant metastases may also be found without manifest regional lymph node metastasis in 30% (33). Mortality rate is 12 to 20% at 5 years and up to 30% at 10 years (Table 2). In a recent review of survival of 194 conjunctival melanomas in the Netherlands, a survival rate of 67% (95% CI, 58.9-76.1) could be shown. Main risk factors for prognosis are localisation (better outcome for unilocular and epibulbar tumours) and tumour thickness (better outcome for tumours < 2 mm Breslow thickness).

Although exfoliative and impression cytology can indicate the diagnosis of melanoma of the conjunctiva, in most cases an excisional biopsy is needed for a correct diagnosis (24). Cytology can demonstrate a conjunctival melanoma with a specificity and sensitivity of 89% and 78% respectively (24, 25). The preparation for a good histopathological assessment is very important in this tumour: the specimens are small and it is sometimes impossible for the pathologist to determine the tumour thickness in tangentional sections (17, 33). Some guidelines for obtaining a good pathology specimen are formulated by Folberg et al (19).

Table 1: *Reported incidence of local recurrences*

		Local recurrences %				
	Ref	*5 years*	*10 years*	*15 years*	*TOTAL*	*n*
Paridaens 1994	(39)	52.3			44.9	256
Missotten 2005	(33)	60.7	66.8	72.2		194
Shields 2000	(43)	26	51	65		150
Werschnik 2002	(52)				51.8	85
Tuomaala 2002	(48)	36	38			85
Lommatzsch 1990	(30)				23.5	81
Anastassiou 2002	(1)	49.3				69
De Potter 1993	(7)				56	68
Desjardins 1999	(8)	40	48			56
Esmaeli 2001	(13)				59	27
Fuchs 1989	(20)	31			31	26

Table 2: *Reported incidence of death of distant metastases in conjunctival melanoma.*

		Metastases %				
	Ref	*5 years*	*10 years*	*15 years*	*TOTAL*	*n*
Paridaens 1994	(39)	17.1	30.1			256
Missotten 2005	(33)	13.7	28.8	32.85		194
Shields 2000	(43)	16	26			150
Tuomaala 2002	(52)	20	38		28	85
Werschnik 2002	(48)	15.2	23	25		85
Lommatzsch 1990	(30)	12.4	23.7			81
Anastasssiou 2002	(1)	32				69
De Potter 1993	(7)				21	68
Desjardins 1999	(8)	23	36			56
Esmaeli 2001	(13)	26	59			27
Fuchs 1989	(20)				31	26

CURRENT THERAPIES AND OUTCOME

Various treatments for primary conjunctival melanoma are available: excision or excision in combination with adjuvant treatment. Adjuvant treatment may consist of intraoperative cryotherapy (7), postoperative brachytherapy (Strontium, Iodine or Iridium) (6, 34, 47), external radiotherapy or proton beam therapy (54) and in a few patients with advanced melanoma primary exenteration (40). Different authors have shown that adjuvant therapy in advanced melanoma reduces the number of local recurrences, although no significantly higher survival could be found (7, 11, 33). As such, a shift has been seen to more adjuvant therapy in the last 2 decades (7, 33).
Intraoperative use of toxic rinsing solutions, to minimise tumour cell spread during the operation and to eliminate melanoma cell seeding, are also reported: alcohol (42), sodium hypochlorite (36), or Mitomycin C (27). The disadvantage of alcohol and Mitomycin C is its toxicity to the corneal epithelium. Up till now, no randomised study has been done to prove the validity of these rinsing solutions in improving the prognosis of the patient.

RECURRENCE

Local recurrence is reported in 30-50% at 5 years, 38-51% at 10 years and 65% after 15 years, depending on patient selection and local treatment (33, 39, 42, 44) (table 1). As such, good local control is recommended. Especially difficult to treat are those conjunctival melanomas, both from the caruncula and deep fornices, that tend to grow into the orbit or via the lacrimal drainage system to the nose (35). In less than 1% conjunctival melanomas will give an intraocular extension (51).
Therefore symptoms like diplopia, nose bleedings, altered smell sensation, epiphora, recurrent dacryocystitis and nasal obstruction should be taken seriously and investigated thoroughly. Current practice is to follow all conjunctival melanoma patients every 6 months until 5 years after the most recent treatment and annually until 10 years.

REGIONAL SPREAD

Locoregional spread usually occurs to the preauricular lymph nodes (7, 13, 52), rarely also to the cervical nodes, submandibular and axillary lymph nodes (33). This is supported by the observation that the sentinel lymph node of conjunctival melanomas is mostly found in the preauricular region (53). Lim et al (29) illustrated that temporal conjunctival melanomas generally spread to the preauricular nodes and nasal conjunctival melanomas to the submandibular nodes, although this is not the rule (29). All patients showing positive axillary lymph nodes also have positive preauricular lymph nodes (33). In some patients with only locoregional spread, early radical neck dissection can prolong survival for up to 15 years (33, 41). This

Table 3: *Proposal for screening in conjunctival melanoma patients.*

CONJUNCTIVAL MELANOMA

Initial screening for metastasis:

- Clinical evaluation of the parotid, submandibular and cervical lymph nodes
- Systemic evaluation (clinical and laboratory examination): Liver function tests, Chest x-ray, Liver ultrasound.
- Sentinel node biopsy in patients with conjunctival melanomas thicker than 2 mm, multiple local recurrences (> 2) or with a diameter greater than 10 mm > If positive, radical neck lymph node dissection.
- Ask for any nose bleeding, alteration in smell sensation, obstructed nose, epiphora.

Follow-up

- Semi-annual follow-up
- Clinical evaluation of the pre-auricular, submandibular and cervical lymph nodes
- Serum tests liver function tests
- Liver ultrasound and chest x-ray in patients with conjunctival melanomas thicker than 2 mm, multiple local recurrences (> 2) or with a diameter greater than 10 mm.
- Ask for any nose bleeding, alteration in smell sensation, obstructed nose, epiphora.

long survival, in the absence of distant metastases, advocates an active search for positive lymph nodes in the preauricular, cervical, and submandibular regions. These data may also advocate consideration of sentinel lymph node biopsy in trying to treat regional metastases at a subclinical stage (3, 12, 15). A therapeutic lymph node dissection may then be performed in patients histologically proven to harbour occult lymph node metastases. It has been shown in cutaneous melanoma that in 99% the sentinel lymph node is indicative for the regional lymphatic spread (18). In cutaneous melanoma, sentinel-node biopsy is recommended as a nodal staging procedure in patients with tumour thickness of 1 mm and more, but the prognostic impact of this procedure has not yet been demonstrated (21, 50). Nevertheless, the new American Joint Committee on Cancer (AJCC) staging system has made SLN biopsy a mandatory procedure (2, 37). In a recent study in skin melanoma nodal metastases could be found 16 months earlier with SNL biopsies compared to clinical observation (37), also showing that early lymphadenectomy gave a better survival than delayed lymphadenectomy. Others prefer to do SLN biopsies only in patients entering adjuvant trials, as overall improvement of survival has not yet been demonstrated in a large randomised trial (28).

Before sentinel lymph node biopsy, Technetium-99m sulfur nanocolloid is injected subconjunctively near the lesion and at the lateral canthus [0.3 mCi technetium-labeled colloid in 0.2 cc] (14). During surgery lymphoscintigrafy is performed to find the sentinel node. Once excised, the sentinel node is sent for histopathology (53) with routine H&E staining and immunohistochemistry for S100, Melan-A or HMB45. Different tumour antigens have been demonstrated on conjunctival melanomas: S100 (both S100A1 and S100B) [63%-100% positive] (22, 26), Melan-A [100% positive], HMB-45 [85% positive], tyrosinase [100% positive] (23), MiTF [91%] (23).

Recent reports give a high percentage of patients with negative SLN biopsy (53); this justifies to perform SLN biopsy only in high risk patients. The indication for sentinel lymph node biopsy is still uncertain, but currently is suggested in conjunctival melanomas thicker than 2 mm, multiple local recurrences (> 2 mm) or with a diameter greater than 10 mm (33, 48). If we use these indications, Tuomaala et al have estimated the positivity range of SLN biopsies at 4 in 10 SLN biopsies (49). Care should be taken to avoid the facial nerve and its branches, as most SLNs are found in the parotid area (16). SLN gives less morbidity and less postoperative complications than radical neck dissection (less lymphedema) (50). On the other hand, rarely, distant metastasis may arise in patients with a negative sentinel node (28).

In case of a positive SLN biopsy, a radical neck lymph node dissection should be planned or a lymphectomy of the pre-auricular and/or submandibular lymph nodes in combination with external beam radiotherapy to surrounding lymphatic drainage areas (47).

Up to now, high resolution ultrasound can not yet replace SLN biopsies due to its limited resolution, especially in the parotid region.

DISTANT SPREAD

Distant spread occurs in 30 % of patients after 10 years (table 2). Although one would expect

that all metastases occur through the lymph vessels to the blood and distant organs, in 26-60% of patients, distant metastases are found without signs of previous or manifest lymph node metastasis (7, 13, 33, 48).
Conjunctival melanoma blood borne metastases usually are found in the liver and the lung (7, 52). Brain, bone (7, 13), skin (33, 47) and peritoneal (52) metastases are also reported. Retrospectively, most distant metastases seem to occur in liver and lung, and screening must focus on these organs.
Most reported risk factor for distant spread and mortality are non-epibulbar localisation of the primary tumour (1) or one of the recurrences (10), and Breslow tumour thickness 2mm.
Treatment for metastasized conjunctival melanoma is the same as for mucosal or skin melanoma, mostly with dacarbazine-DTIC or INF-alpha-2b therapy, sometimes combined to BCG and recombinant interleukin-2, but the prognosis is poor and in general survival time is short.

DISCUSSION

Up to now, no protocols are published for screening in conjunctival melanoma. Nevertheless, as early detection of lymph node metastases may improve the life expectancy considerably, screening for conjunctival melanomas metastases is recommended. Increasing experience with sentinel lymph node biopsies will give us more reliable criteria for the indication of this test in conjunctival melanoma.
In contrast with uveal melanomas, no tumour doubling times are estimated at the moment for conjunctival melanoma. Consequently it is difficult to estimate the frequency of any follow-up protocol. In conjunctival melanoma the frequency of follow-up controls is highly influenced by the presence or absence of PAM with or without atypia. We suggest a screening at 6 months for local recurrences and questioning for nasal bleeding or dacryocystitis, combined with clinical investigation of the eye and the lymph nodes, and this for the first 5 years (table 3). Most metastases occur in the first 5 years after treatment of the primary tumour (33, 48).
Distant metastases are mostly confined to the liver and chest and screening should focus on liver ultrasound and chest X ray. But, as metastases are reported at many other localisations, serum screening may be more useful.
Currently, research is under way to investigate the relevancy of serum tests in screening for conjunctival melanoma. Recently, the prognostic value was shown of S100 and MIA in screening of both uveal and skin melanoma, but this has not been examined for conjunctival melanoma (31, 32, 34). Techniques for demonstrating tyrosinase of Melan-A positive circulating tumour cells have been improved recently, and may contribute to the early detection of distant metastases.
Although none or little information is available on the treatment of metastatic conjunctival melanoma, one can assume that these patients will react positively to skin melanoma regimens, in contrast with the experiences in uveal melanoma.

CONCLUSION

The most important factor in improving survival of conjunctival melanomas is the systematic investigation for regional lymph node metastases, and probably the use of sentinel node biopsies in high risk patients (tumour height 2 mm, diameter larger than 10mm, multiple recurrences). Although little information is available on distant metastases, lung and liver seem to be the most important first localisations, and screening with liver ultrasound, serum tests and RX thorax may be advised every 6 months. The sensitivity of serum tests for S100 and MIA are momentarily under investigation in conjunctival melanoma.

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