Article is available online at http://www.webio.hu/por/2003/9/1/0007

REVIEW

Malignant Mucosal Melanoma of the Head and Neck – a Review

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Mucosal melanomas comprise about 1% of all malignant melanomas and exhibit far more aggressive behaviour than that of skin melanomas: they are more inclined to metastatize into regional and distant sites or recur locally, regionally or in distant locations, resulting in a high rate of cause-specific death. Mucosal melanomas in the head and neck region account for half of all mucosal melanomas, occurring mainly in the upper respiratory tract, oral cavity and pharynx. They appear with equal gender distribution and with a peak incidence in the age range 60-80 years. In consequence of their hidden location, they are usually diagnosed in a locoregionally advanced clinical stage, with a rate of 5-48% of regional and 4-14% of distant dissemination. The typical therapeutic approach is surgery, postoperative irradiation and systemic therapy. Local control with either surgery or radiotherapy is frequently (60-70%) achieved, but the rates of local, regional and distant recurrences are high (50-90%, 20-60% and 30-70%, respectively). The reported 5-year actual survival rates are poor (17-48%), which is attributed mainly to a haematogenous dissemination. These characteristics demonstrate that identification of the precursor lesions and more effective local and systemic approaches are needed to improve the therapeutic results. (Pathology Oncology Research Vol 9, No 1, 7–12, 2003)

Keywords: head and neck; mucosal melanoma, malignant melanoma; surgery radiotherapy; chemotherapy

Introduction

Malignant mucosal melanomas arise mainly from the mucous membranes of the head and neck, the female genital organs or the anorectal and urinary tracts. They have a neuroectodermal origin, which is the reason for their low occurrence in the epithelial lining of endodermal origin (e.g. the oesophagus, larynx, nasopharynx, etc.).[21] Mucosal melanomas are rare: 1074 such cases were reported up to 1994.[11] The National Cancer Data Base (NCDB), USA registered a total of 84 836 patients with cutaneous or non-cutaneous melanomas between 1985 and 1994; approximately 1.3% of them were in mucosal surfaces. The distributions mucosal melanomas in the head and neck, female genital, anorectal and urinary tract regions were 55%, 18%, 25% and 3%, respectively. The lymphatic status was recorded in 28% of the entire cohort, and 40% of the patients had positive nodes. The rates of positive lymph nodes for mucosal melanomas of the head and neck, female genitals, or anorectal and urinary tracts were 27%, 23%, 61%, and 11%, respectively.[11]

Interestingly, mucosal melanomas are generally more frequent in populations where the incidence of cutaneous melanoma is low.[38] Thus, the proportion of mucosal melanomas is higher (8.8%) in African-American and Hispanic patients, than in the general population (1.3%) of the USA.[11] The prevalence of mucosal melanoma also reveals significant geographical differences.[33] In Japan and Uganda, for instance, it is a relatively frequent disease.[9, 40, 46, 49]

Similarly to cutaneous melanomas[33], mucosal melanomas affect women more commonly (64%) than men, mainly because there is no male counterpart for vulvovaginal lesions.[11] At the same time, there is no gender difference as concerns the occurrence of mucosal melanomas in the head and neck region.[9, 41] The peak age at diagnosis is higher for mucosal (70-79 years) than for cutaneous melanomas (45-55 years).[33]

The precursor lesion for mucosal melanoma has not yet been identified, but atypical melanocytic hyperplasia and coexistent melanosis (*Figure 1*) may be predisposing dis-

Received: Jan 28, 2003; *accepted:* March 13, 2003

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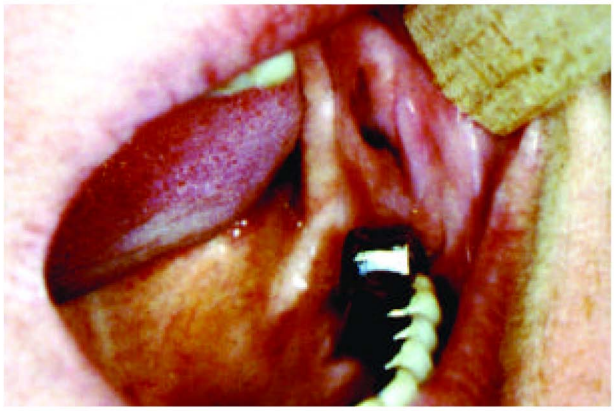

Figure 1. *The precursor lesion for mucosal melanoma located in the lower gingiva*

eases.[49] Takagi et al.[49] distinguish 2 types of melanosis in the oral cavity: pre-existing or concurrent melanosis (an increased number of melanocytes in the basal layer with atypia) associated with malignant melanoma, and melanosis without detectable atypia which is not associated with melanoma. It is presumed that congenital pigmented spots may develop into melanomas in parallel with the hormonal changes in the pubertal period.[22] Mucosal melanomas are not related to dysplastic junctional naevi as their cutaneous counterpart.[27,51]

The pathological diagnosis of malignant mucosal melanomas is based on the demonstration of intracellular melanin, tyrosinase activity and the presence of premelanosomas. Immunohistochemically melanomas react positively to antibodies of HMB-45, S-100 protein, MART-1/Melan A, vimentin and NKI/C-3.[39,47] In clinical practice the prognostic significance of serum LDH, S-100B protein and 5-S-Cysteinyldopa is not clear enough in patients with metastatic malignant melanoma. The elevated marker levels correlated well with the disease progression and survival.[3,7,50]

Mucosal melanomas are characterized by multiplicity, satellite formation, local and angiolymphatic invasion, consecutive pronounced local, regional and distant dissemination and a high rate of cause-specific death.[5,32,45] The standard primary treatment is surgical, in spite of the frequent local recurrences and regional or distant spread. In a majority of the cases, radiotherapy and systemic therapy have been used as palliative modalities, though there is evidence of their occasional beneficial effect.[19, 34-35,46]

Mucosal melanomas of the head and neck

Mucosal melanomas of the head and neck (*Table 1*) comprise about half of all malignant melanoma cases,[11] and > 20% of all melanomas of the head and neck.[45] The first cases in the English literature were reported in 1885 by Lincoln; since that time, over 1000 patients have been reviewed.

These melanomas occur mainly in the upper respiratory tract (56%) and oral cavity (44%).[6] Within the oral cavity, the most common site is the hard palate (up to 80%), followed in decreasing frequency by the upper and lower gingiva and bucca (*Figure 2*). Mucosal melanomas in the nasal cavity and paranasal sinuses are very rare,[40] and they are extremely seldom found in pharyngeal, laryngeal or oesophageal locations.[23,39]

Because of the rarity of the disease, reports on large patient groups (*Table 2*) with mucosal melanomas in the head and neck region are infrequent.[13,18-19,23,25,36,38-39,45-47] It is noteworthy that nearly one-third of mucosal melanomas in the head and neck region are amelanotic[19], while approximately 10-15% of all melanomas with a hidden location are amelanotic[20] and are usually diagnosed in a locoregionally advanced clinical stage.[5] In most of the published series, the duration of the symptoms was reported to be 1-5 months.[18, 30, 47]

The most frequent symptoms in patients with sinonasal melanomas are epitaxis, nasal obstruction and diplopia or proptosis (especially in cases of locally advanced tumors). Patients with melanomas in the oral cavity generally have symptoms related to pigmented masses, ill-fitting dentures or ulceration.[39]

Mucosal melanomas of the head and neck exhibit far more aggressive behaviour than melanomas on the skin; they are more inclined to metastasize into regional and distant sites or recur locally, regionally or at distant locations. At the time of presentation and during the clinical course, cervical lymph node metastases were observed in 5-48% of the cases.[11,15,18,23,25,38,45] The highest rate (48.3%) of regional metastases was reported from India.[38] In this series, the duration of the clinical symptoms was generally 3 months and the majority of the patients were in an advanced stage. This may suggest that this series involved more asymptomatic and hidden tumors and fewer nasal cavity and oral cavity lesions or symptomatic lesions. In the NCDB report, the frequency of lymph node metastasis in patients with skin melanomas was about 9%.[11] At the time of presenta-

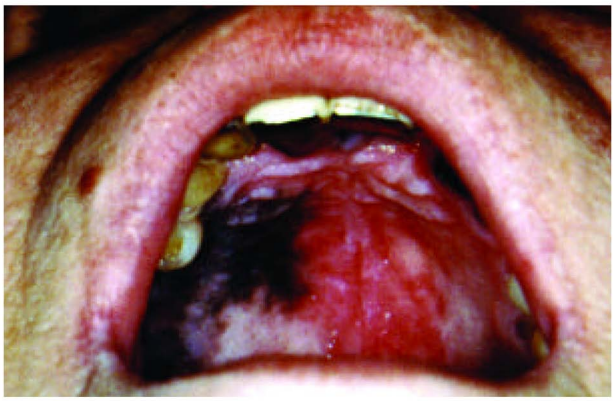

Figure 2. *Recurrent mucosal melanoma of the hard palate*

Table 1. Comparisons of mucosal and skin melanomas of the head and neck

	Mucosal melanoma of the head and neck	*Skin melanoma*
Occurrence among melanomas	1%	95%
Geographical distribution	with a low incidence of skin melanomas	with a low incidence of mucosal melanomas
Female : male distribution	1 : 1	a slight female dominance
Peak age at diagnosis	60-80 years	40-50 years
Precursor lesion	atypical melanocytic hyperplasia with coexistent melanosis? congenital pigmented spots?	dysplastic junctional nevus
Locoregionally advanced disease (stage III-IV)	80%	5%
Amelanotic appearance	33%	5%
Initial regional dissemination	5-48%	10%
Initial distant spread	4-14%	4%
Rate of local recurrence	50-90%	6-50
Rate of regional recurrence	20-60%	20-33%
Rate of distant dissemination	30-70%	13-15%
Mean 5-year survival rate	17.1% (range 0-48%)	81-85%

tion, the incidence of distant metastasis was reported to be 4-14% for mucosal melanomas[18,23,38,45,47] and 5.3% for skin melanomas.[11]

The actuarial 5-year survival rates of the most important series with different treatment modalities are listed in *Table 2*. Cutaneous melanomas had a mean survival rate that was higher (81-85%)[11,33] than that (17.1%) for mucosal melanomas.[11,13,19,23,36,38-39,45-47] The reported 5-year disease-specific survival rate is significantly better ($p<0.05$) for mucosal melanomas of the head and neck than for female genital or anorectal melanomas,[11,18-19,23,27,36] which may be ascribed to the greater difficulties in diagnosing hidden foci in the genital and anorectal regions. The survival curves demonstrate a continuous decline up to 5 years, without plateau formation, and recurrences may occur even 10-15 years after the primary therapy in some patients.[18,23,47] The characteristics of the survival curves are explained by the very different possible clinical courses of malignant melanomas, ranging from the highly-malignant, aggressive disease to a relatively low-grade tumor.

Identification of prognostic factors of the cause-specific survival is difficult, as only small retrospective studies have been performed in which different treatment modalities were applied. In most studies, the age, the gender and the location of the primary focus did not prove to be significant prognosticators. Only in one study[23] was the reported survival rate better in females (31%) than in males (9%). In the NCDB report,[11] the presence of positive lymph nodes was associated with a poorer survival (16%), than in the event of negative histopathological findings (39%). Patel et al. found that an advanced stage (a tumor thickness of 5 mm, or the presence of vascular invasion and nodal/distant metastases) is a significant adverse prognosticator for cause-specific survival on univariate analysis.[39] It is sometimes very difficult to utilize these observations, e.g. Shah et al. reported on 74 patients in whom nearly all the primary lesions displayed intralesional lymphatic or blood vessel invasion.[45] Local recurrences play an important role in the cause-specific survival as there is a direct relationship between their occurrence and the development of distant metastases.[30, 47] During the clinical course, the rates of local, regional and distant recurrences (50-90%, 20-60% and 30-70%, respectively) are high in patients with mucosal melanomas of the head and neck as compared with the corresponding rates for skin melanomas.[23,38,39,40]

The most important treatment modalities for mucosal melanomas of the head and neck are surgery, irradiation and systemic chemo/immunotherapy (*Table 2*). The 5-year cause-specific survival probabilites increase (up to 48%) on application of all the above-listed treatment modalities (*Table 2*). Surgery is the primary treatment modality for

localized mucosal melanomas, irrespective of the involvement of the regional lymph nodes.[19, 27] In consequence of presence of surrounding vital structures, positive surgical margins are common. This results in a consecutive high rate of local recurrences, e.g. 50-90% of the patients with tumors in the nasal cavity and paranasal sinus experience a local relapse postsurgically, even following postoperative radiotherapy.[41,45,51] Local recurrences are also related to satellite formation, angiolymphatic invasion and a submucosal spread.[32,45,51] Neither local control nor survival is affected by negative surgical margins, but wide surgical resection is recommended, with preservation of vital structures whenever possible.[27] Guzzo reported on 48 cases with mucosal melanomas in the head and neck region, most of whom were treated by surgery alone.[23] The 4-year disease-free rate and the observed 5-year survival rate for this cohort were only 7%, and 21%, respectively. In 13 surgically-treated (with or without radiotherapy) cases of nasal and paranasal sinus melanoma, the 5-year actuarial survival rate was 20%.[27]

Prophylactic neck dissection is not recommended, as mucosal melanomas in the head neck region generally metastasize to the regional lymph nodes less frequently than do squamous carcinomas in the same region.[41]

The role of radiotherapy in the treatment of mucosal melanoma is not clearly defined.[27] There has been a dogma that malignant melanoma is radioresistant.[27,45] Some *in vitro* radiobiological[4] and clinical studies,[2,19,27,36,39,41,46,52-53] however, have demonstrated that radiotherapy may have a beneficial effect in locoregional control. The clinical studies were based on the *in vitro* investigation by Barranco[4], which revealed a large, curvy shoulder with a relatively steep terminal slope in the survival curves of three human melanoma cell lines. These observations indicate a large capacity for the accumulation of sublethal damage induced by doses up to 4 Gy and comprise a basis for the use of hypofractionated radiotherapy in malignant melanoma.

In clinical studies involving external photon beam irradiation, higher rates of complete or partial responses can be achieved by applying a high dose (3-8 Gy) per fraction, as compared with conventional fractionation (1.8-2 Gy/fraction) schemes.[2,19,41,52-53] Different fractionation schedules have been used, e.g. 5 x 6 Gy twice a week[2], 8 x 5 Gy/twice a week,[41] or 4 x 8 Gy once-a-week. Gilligan et al treated 28 cases of sinonasal melanoma by radical external irradiation (3-3.5 Gy/fraction, with a total dose of 50-55 Gy over 15-16 days) and achieved a crude 5-year survival rate of 18%.[19] However, an increasing rate of late toxicity of normal tissues is expected following hypofractionated radiotherapy.[2,19,24,33] As a high incidence of radiation-induced late sequelae of the normal tissues is a current unacceptable complication, the radiobiological advantages of hypofractionation are not fully exploitable.

Besides external photon/gamma beam therapy, other irradiation modalities are also available. Shibuya et al.[46] reported a local control rate of 79% in 28 patients with upper jaw melanomas (mainly stage I), who were treated via an intraoral mould (^{60}Co, ^{192}Ir, or ^{198}Au with a total dose of 72-120 Gy in 5-10 days), with an intraoral electron beam (with a total dose of 70-80 Gy in 7-8 fractions) or with interstitial brachytherapy (^{198}Au, 90 Gy).

In spite of its beneficial effect, radiotherapy is usually applied as an adjuvant modality reserved for positive sur-

Table 2. Clinical characteristics of reported cases of malignant mucosal melanoma in the head and neck region

Author	*No. of cases*	*Tumor location*	*Treatment modalities*	*5-year overall survival rate (%)*
Gilligan (19)	28	Sinonasal	Radiotherapy	18
Shibuya (46)	28	Upper jaw	Radiotherapy +/– surgery	25
Shah (45)	74	Head and neck	Surgery +/– radiotherapy	22
Chaudhry (13)	41	Head and neck	Surgery+/– radiotherapy+/– chemotherapy	17
Lund (36)	58	Sinonasal	Surgery+/– postoperative radiotherapy+/ –chemotherapy (BCG, melphalan)	28
Pandey (38)	60	Head and neck	Surgery+/– radiotherapy+/– chemotherapy	28*
Chang (11)	163	Head and neck	Surgery+/– radiotherapy+/– chemotherapy	32
Patel (39)	59	Sinonasal and oral	Surgery +/– postoperative radiotherapy+/ –chemotherapy	35
Stern (47)	42	Sinonasal and oral	Surgery+/– radiotherapy+/– chemotherapy+/ –immunotherapy	40
Guzzo (23)	48	Head and neck	Surgery+/– radiotherapy+/– chemotherapy+/ –immunotherapy	21

*3-year survival

gical margins, local recurrence or palliation. The role of postoperative local radiotherapy, however, is not settled: statistical analysis has not confirmed that surgery with additional radiotherapy improves the patient's overall survival significantly.[36,39] Lund et al. examined 58 patients with sinonasal malignant melanomas and found no difference in local control or survival between patients treated with surgery alone and those receiving surgery and conventionally fractionated radiotherapy.[36] Prophylactic nodal irradiation is not recommended[19] for the same reason as indicated previously in connection with the avoidance of prophylactic surgical dissection.

Chemo/immunotherapy is used with an adjuvant or palliative intention.[23,41] It is useful as adjuvant therapy, but it does not seem to influence the overall cause-specific survival rate.[8,39] With a palliative intention, chemo/immunotherapy furnishes disappointing results; this may be explained in part by the fact that there is no lymphocytic infiltration around the tumor, suggesting an immunodeficiency and consecutive immunological non-respondence. In selected cases, however, cryosurgery may increase the lymphocyte activity, and this immunologic stimulation may improve the survival rates of the patients.[5]

The most frequently used chemotherapy agents are dacarbazine, the platinum analogs, the nitrosoureas and the microtubular toxins. Dacarbazine represents the conventional therapy of metastatic melanomas at this time, although the response rate is only 14% to 20%, the median response duration is 4 to 6 months and less than 2 % of patiens survive 6 years.[33] In small, randomised trials that compared the dacarbazine alone and with a combined with either tamoxifen or IFN-α_2. The latter two produced higher response rate than dacarbazine alone,[14,16] but phase III ECOG trial failed to prove it.[17] Chemotherapeutic agents in various combination have been used in the treatment of stage IV patients. In phase II trials,[29,31] two of the most effective combinations (produced response rates ranging from 30 to 50%) were the three-drug combination of cisplatin/vinblastine/dacarbazine (CVD) and the four-drug combination (Dartmouth combination) of cisplatin/dacarbazine/carmustine and tamoxifen (CDBT). Although in randomized phase III trials showed no differences in either response duration or survival.[1,12] Temozolomide is administered usually in CNS melanoma, because this is able to penetrate to the central nervous system.[10,37]

Immunotherapy currently is effective only in a small percent of patients with malignant melanoma. The first identified immunotherapeutic agent was IL-2, producing complete response only in 6 percent of patients. Using high-dose IL-2 (720,000 IU/kg) alone appears to be more effective than low-dose IL-2.[48] In numerous trials IL-2 has been used alone or in combination with other cytokines (IFN-α, IL-1, IL-4, IL-12, TNF, TNF-γ, and FLT3L) and with other chemotherapeutic agents (cisplatin, dacarbazine, carmustine, vinblastine). None of these combinations was associated with enhanced survival rate.[28,33,44] In an EORTC study patients with metastatic disease were treated with IL-2 and IFN-α alone and in a combination with cisplatin. Increased response rate (18% vs 35%) was found, when IL-2 and IFN-α with cisplatin were used.[26] When chemotherapy was followed by IFN-α2b, and IL-2 survival was not affected but toxicity was higher.[44]

The presence of paraneoplastic vitiligo or leukoderma predicts response to immunotherapy.[43] Various immune effectors such as LAK cells, tumor-infiltrating lymphocytes (TILs) or activated T cells combined with IL-2 and IL-2 alone have been tested, but no difference in response rate or survival was evaluated.[42]

In view of the clinical characteristics of mucosal melanomas of the head and neck, early detection of the tumor through identification of the precursor lesions and more effective local and systemic approaches are needed to improve the therapeutic results.

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