Oral Malignant Melanoma

Thomas Mücke, Anna Borgmann, Klaus-Dietrich Wolff and David Andrew Mitchell

Department of Oral and Maxillofacial Surgery, Technische Universität München, Klinikum Rechts der Isar, Germany

1. Introduction

It is generally accepted that the outcome of oral malignant melanoma is worse than that of cutaneous and systemic head and neck melanoma. The five-year survival reported in the literature for oral melanomas varies from 0 - 20 % (Liversedge, 1975, Rapidis et al., 2003, Rapini et al., 1985), whereas the overall survival for head and neck melanomas ranges between 20 and 48 % (Guzzo et al., 1993, Patel et al., 2002, Stern and Guillamondegui, 1991, Temam et al., 2005), confirming anatomical site specific variation.

Treatment modalities for primary oral melanoma include surgical resection with or without neck dissection. Adjunctive modalities such as immunotherapy, chemotherapy and radiation therapy may offer a supportive but as yet non curative role. The mainstay of curative treatment is surgery, mandating complete resection of the tumor with clear margins if possible (Rapini et al., 1985, Umeda and Shimada, 1994). Immunotherapy and chemotherapy are techniques which are the subject of controlled trials or palliation (Mendenhall et al., 2005). The rarity of oral malignant melanomas means that to date no randomized clinical trials have been conducted to establish an evidence base in the literature to provide comparisons of treatment modalities. The efficacy of surgery with planned supplementary radiotherapy remain unresolved and continue to generate controversy (Patel et al., 2002).

Due the rarity of this disease, there is a lack of consistency in immunohistochemical confirmation of the diagnosis, staging strategies and treatment planning as diagnostic techniques and treatment have evolved over recent years in melanoma is other body sites and attempts have been made to translate these to the much rarer oral melanoma. This book section would like to aid the reader in understanding the current state of etiology, epidemiology, and treatment modalities of this very rare but aggressive tumor entity.

2. Oral malignant melanoma

The diagnosis of oral malignant melanoma often remains difficult. Differential diagnoses should include benign as well as malignant lesions and exogenous pigmentation can be often found (Figure 1). It also needs to be borne in mind that amelanotic malignant melanoma can affect the mouth, comprising one third of all oral malignant melanomas.
Fig. 1. Oral pigmentation due to inoculation of amalgam after dental treatment in the left buccal mucosa.

The histological spectrum of benign pigmentations is wide: macular hyperpigmentation caused by junctional proliferation with or without cellular atypia, melanocytic naevi (Figure 2), such as junctional, compound, subepithelial, blue and combined naevi. Other causes of oral pigmentation include: race, Peutz-Jeghers syndrome (Daley and Armstrong, 2007), Laugier-Hunziker syndrome (Mowad et al., 1997), Addison´s disease (Lamey et al., 1985), patients with pulmonary diseases, especially in lung cancer (Merchant et al., 1976), and hemosiderosis.

Fig. 2. Melanocytic naevi in the upper left vestibule.
Some authors describe a preexisting oral pigmentation for several month or years in one third of all patients with a primary oral malignant melanoma (Chaudhry et al., 1958, Liversedge, 1975, Rapini et al., 1985), although others found no correlation (Meleti et al., 2007). The appearances of oral malignant melanomas vary and should always be considered in oral lesions without the tendency to heal (Figure 3). Remember that about 1/3 of all oral malignant melanomas are not pigmented (Anneroth et al., 1973, Chaudhry et al., 1958, Greene et al., 1953, Lengyel et al., 2003, Liversedge, 1975, Rapidis et al., 2003).

Fig. 3. Intraoral view of a malignant melanoma arising from the palate.

2.1 Etiology
Melanomas are categorized into four different types according to anatomic region and pathological factors: 1. melanomas arising from skin without chronic sun damage, 2. melanomas on skin with chronic sun damage, 3. acral melanomas, and 4. mucosal melanomas (Curtin et al., 2006). The etiology of primary oral malignant melanoma is still unknown. Cigarette smoking, denture irritation and alcohol have been mentioned as possible risk factors, but evidence remains obscure. Intraoral malignant melanomas arise from melanocytic cells of the oral cavity, which represent a minority of all cells of the mucosal membrane. Although just a few melanocytes are present in the oral mucosa the potential to develop malignant melanomas clearly exist. Indeed it is recognized that malignant melanoma can very rarely develop in almost any organ suggesting that circulating melanocytes may be responsible. About 5-30 % of primary malignant melanomas are preceded by oral pigmnetations for months or even years. It has been suggested that melanosis represents the initial phase characterized as the radial phase of growth and precedes the invasion of underlying tissues (vertical growth) by years, however the histological spectrum of benign pigmented lesions is wide and a pre-existing pigmented lesion is not usually associated with mucosal melanomas. Most arise as new lesions, from apparently healthy mucosa.
Malignant melanomas develop from melanocytes derived from the neural crest. The most frequently primary sites in the oral cavity are the palate and maxillary gingiva (Barker et al., 1997, Hicks and Flaitz, 2000, Lee et al., 1994). Mucosal melanomas are considered to be more aggressive tumors compared with cutaneous melanomas and they are more inclined to metastasize into regional and distant sites, recur locally or regionally resulting in a high rate of disease specific-death.

2.2 Epidemiology
Malignant melanoma in the head and neck area is rare. Oral cavity primary malignant melanoma comprises 6.3% of all melanomas in the head and neck area and only about 0.7–1.6% of all melanomas arise in the oral mucosa (Chang et al., 1998, Moore and Martin, 1955). The incidence of primary mucosal melanomas of the head and neck is approximately four per 10 million population per year (Hicks and Flaitz, 2000). The most frequently affected oral sites are the palate and maxillary gingiva (Barker et al., 1997, Hicks and Flaitz, 2000, Lee et al., 1994). The incidence in Japan is much higher than in western countries, in which it occurs with less than 1% (Batsakis, 1982, Brandwein et al., 1997, Umeda and Shimada, 1994). The age of the patients varies between 20 and 80 years, the mean age reported in the literature ranges from 56 to 66.5 years (Gorsky and Epstein, 1998, Hicks and Flaitz, 2000, Patel et al., 2002, Rapidis et al., 2003, Rapini et al., 1985) and a modest male preponderance has been described (Rapini et al., 1985).

2.3 Prognosis
The prognosis is adverse. Due to delayed diagnosis early invasion of surrounding tissue, local lymph node involvement and distant metastasis, the prognosis of oral mucosal melanomas is very poor. The reported 5-year survival rates vary in the literature between 6 and 18% but also between 45 and 48% (Enroth CM, 1975, Lee et al., 1994, Lund, 1993, Ravid and Esteves, 1960, Stern and Guillamondegui, 1991). Gingival melanoma has a slightly better 5-year survival rate (18%) than that of palatal melanoma (11%), with a longer median survival period (46 months vs. 22 months). These wide variations are probably due to the fact that comparable classifications are still not agreed internationally. The routine use of tumor thickness of mucosal melanomas, as described by the Breslow or the Clark levels are not widely performed as a routine method in everyday experience (Prasad et al., 2003, Prasad et al., 2002, Thompson et al., 2003). Therefore an evidence base derived from histopathological assessment and subsequent prognosis for malignant mucosal melanomas is lacking. Despite this many reports show a correlation between tumor thickness and prognosis (Mücke et al., 2009, Prasad et al., 2004). Many authors agreed that the survival rate was not only closely related to the stage of the tumor, but the treatment that patients received (Mücke et al., 2009, Prasad et al., 2003, Prasad et al., 2004, Rapidis et al., 2003, Rapini et al., 1985, Tanaka et al., 2004, Temam et al., 2005).

The vast majority of the head and neck mucosal melanomas are Stage 1 at the time of presentation, Prasad et al defined a 3-level-microstaging system, which represents different microanatomical compartments separated by tissue barriers. They found out that this microstaging system is prognostically significant and an independent predictor concerning the 5-year survival rate and the recurrence-free survival (Mücke et al., 2009, Prasad et al., 2004). In 2009, the American Joint Committee on Cancer (AJCC) Melanoma Staging Committee used previously published guidelines and determined criteria which were used
in the TNM classification and the stage groupings (Balch et al., 2009). These criteria are established for all kinds of melanomas and are proposed as follows:

1. In patients with localized melanoma, tumor thickness, mitotic rate, tumor burden, and ulceration were the most important prognostic factors.
2. The mitotic rate indicates the level of invasion as a primary criterion for defining T1b melanomas.
3. Components that defined the N category were the presence and number of metastatic nodes of the primary melanoma.
4. All patients with microscopic nodal metastases, regardless of extent of tumor burden, are classified as stage III.
5. On the basis of a multivariate analysis of patients with distant metastases, the two dominant components in defining the M category continue to be the site of distant metastases and an elevated serum lactate dehydrogenase level.

Factors that have been associated with worse disease-specific survival include clinical stage at presentation, thickness of the tumor, tumor burden at the time of staging (microscopic vs. macroscopic), presence or absence of primary tumor ulceration, presence of vascular invasion, melanosis, and development of nodal and distant metastasis (p < 0.001) (Balch et al., 2009). Multiple local recurrences are the most common cause of treatment failure and may occur 10-15 years after primary treatment. The most common sites of distant metastases include the lungs, brain, liver and bones.

2.4 Staging

The criteria to verify the presence of a primary intraoral melanoma are:

1. demonstration of clinical and microscopic tumor in the oral mucosa
2. presence of junctional activity in the lesion
3. inability to show any other primary site.

All patients have to fulfill all these criteria to verify the diagnosis of primary oral malignant melanoma (Greene et al., 1953). In addition to the standard staging procedure, patients should be observed by means of: sonography, gastroscopy and bronchoscopy in order to exclude other potential primary sites and confirm by exclusion the diagnosis of primary oral mucosal malignant melanoma (Mücke et al., 2009). It is important to confirm the comparatively rare finding of primary oral mucosal malignant melanoma is supported by exclusion of other potential mucosal sites for example the respiratory and the gastrointestinal tract, which are more frequently found than oral melanomas (Lee et al., 1994, Mendenhall et al., 2005, Prasad et al., 2003).

Patients should be staged according the TNM Melanoma Staging System of the American Joint Committee on Cancer which includes in the staging the extent of the tumor status as well as the extent of the nodal status, but does not provide a specific guideline for oral mucosal melanomas. Therefore a simplified staging system has been established, which classifies tumors in 3 stages: Stage I to localized disease, confined to the primary site, stage II the primary lesion with cervical lymph node metastasis and stage III for distant metastasis. As previously described there is a 3-level-microstaging system which relates to the prognostic outcome. In this system each level represents a microanatomical compartment, which is defined through tissue barriers. Breach of each barrier correlates with a progressively worse survival rate. Level I is defined as an in situ mucosal melanoma or microinvasion, Level II as an invasion limited to lamina propria and Level III is defined as melanoma with a deep invasion into surrounding tissue such as bone cartilage or skeletal muscles.
2.5 Histopathology
The surface architecture from oral melanomas ranges from macular to ulcerated and nodular. As recommended at the WESTOP (Western Society of Teachers of Oral Pathology) Banff Workshop, oral malignant melanomas should be separately considered from the cutaneous forms and proposed to subclassify them according to the histological pattern into: in situ melanoma, invasive, combined (invasive melanoma with in situ components) and atypical melanocytic proliferation (in case where diagnosis is equivocal) (Barker et al., 1997). In situ melanomas are limited to the epithelium and the epithelial-connective tissue interface, and represent 15% of the oral melanomas. They show a proliferation of atypical melanocytes characterized through hyperchromatic and angular nuclei with infrequent mitotic activity. The melanocytes may be arranged irregularly at the epithel connective tissue-interface or may be distributed in aggregates.

Invasive pattern in which the melanoma extend into the connective tissue is represented in 30% of oral melanoma, showing a wide range of cell types including spindle, plasmocytoid, clear cells and epithelioid, arranged into sheets or organoid/alveolar formation. The large and vesicular nuclei appear frequently with prominent nucleoli and rare mitosis. 55% of oral melanomas having combined pattern, which is typical for advanced lesions (Barker et al. 1997, Femiano et al. 2008).

In most instances melanomas contain melanin pigmented tumor cells but amelanotic melanoma show a lack of melanin production, which exacerbates the correct diagnosis, because amelanotic melanoma can mimic a variety of poorly differentiated carcinoma or cell lymphoma. For distinguishing these melanomas from other tumors immunohistochemical stains have been proven to be helpful. For differential diagnosis, it should be claimed that immunhistochemical staining of the following markers is mandatory and the basis of the diagnosis of an oral malignant melanoma.

Immunohistochemical markers include S-100 protein, gp100 (HMB-45) and Mart-1 (Melan-A) (Messina et al., 1999). These markers are also used for the identification of micrometastases in lymph nodes (Messina et al., 1999). The Antibody HMB-45 reacts with the melanosomal glycoprotein gp100, showing a positive staining in active early melanosome formation and showing epithelioid lesions intensely immunoreactive for HMB-45. It is considered as more specific but less sensitive than the S-100 protein, an acidic calcium binding protein, which is a very sensitive marker for nevus and melanoma cells, and even spindled lesions appear intensely immunoreactive for S-100 protein (Blessing et al., 1998, Gazit and Daniels, 1994). Melan-A is considered to be specific for melanoma cell lines, as a product of the MART-1 gene it is a melanocytic differentiation marker which is recognized on melanomas as an antigenic target of T lymphocytes (Kawakami et al., 1994).

In recent years some molecular markers, like the Ki67 antigen emerged as potentially prognostical indicators, however the role of potential therapeutic relevance of KIT inhibitors in mucosal melanoma further needs to be investigated.

2.6 Therapy
Regarding the treatment of the four types of melanomas, melanomas arising from skin without chronic sun damage, melanomas on skin with chronic sun damage, acral melanomas and mucosal melanomas, most authors agree that radical ablative surgery with wide local excision of the primary lesion and dissection of metastatic lymph nodes are the basis of every curative therapy (Curtin et al., 2006). Controversial points are the margin of
the excision, the optimal time to dissect the local lymph nodes, and the uncertainty of the extent of lymph nodes dissection. Surgery is the mainstay of treatment but can only be accomplished if vital parts of the body are not affected and therefore anatomical limitations often make a radical excision impossible.

The following protocol refers to the extent of margins:
1. Excision of the primary lesion including at least 1 – 2 cm of healthy tissue based on the primary tumor extent and thickness
2. Lymph node dissection and removal of lymph node metastases
3. Consideration of radiochemotherapy (limited evidence as to the benefit of postoperative radiotherapy exists for other anatomical sites).

2.6.1 Surgery
Principles defined by the first tumor resection in 1857 remain viable today in that the treatment of all melanomas should be performed by wide resection. Cutaneous melanomas are still treated by that principle to avoid local recurrence (Essner, 2003, Hauschild et al., 2003, Veronesi and Cascinelli, 1979). Limited excision of the primary lesion as well as excisional and incisional biopsies are associated with an increased risk of causing accidental dissemination of malignant cells within the adjacent tissues or even into the blood or lymphatic stream with probable devastating consequences (Harter et al., 1992, Kusukawa et al., 2000).

The surgical margin also depends on the thickness of the tumor. In patients with tumors less than 1 mm thickness, a surgical margin of 1 cm has been shown to be adequate, compared with wide tumor margin resections of 3 cm (Veronesi et al., 1988). None of these patients developed local recurrence in the follow-up period revealing an adequate resection extent. In patients with tumor thickness of 1 to 2 mm local recurrences were found in both study groups of patients receiving resection margins of 1 cm or 3 cm without significant differences, although more recurrences were found in the 1 cm group (Veronesi et al., 1988). The evidence, that resections of 1 to 2 cm around the tumor are sufficient and show similar results in local control and overall survival, have been also found by other studies comparing the long term results of different resection protocols in varying tumor extent and thicknesses (Balch et al., 1993, Heaton et al., 1998). The local recurrence rate in these studies is 1.7% with 2 cm surgical margin compared with 0.8% with 4 cm after six years without statistically significant differences (Balch et al., 1993, Heaton et al., 1998). The surgical therapy within the oral cavity remains problematic because wide resection margins require also reconstruction techniques after tumor ablation to avoid mutilation, functional impairment and a poor quality of life (Mücke et al., 2009, Mücke et al., 2011, Mücke et al., 2010). In some instances the suggested resection margins would compromise vital structures which mean a compromise between theoretically ideal margins and postoperative function and quality of life must be made.

Regional lymph nodes are the most common sites of metastases for all melanomas. Palpable lymph nodes in the neck or fixed to the adjacent tissues should be suspicious for metastases. Radiologically, lymph nodes larger than 1 cm must also be considered to be involved by metastases. There exists a correlation between the tumor thickness and the occurrence of regional lymph node metastases. Primary lesions less than 1 mm thickness are considered to yield a rate of < 10% lymph node metastases, 1.01 to 2.00 mm are accounting for about 20%, 2.01 to 4.00 mm are accounting for 33%, and >4.00 mm are associated with a risk of
lymph node involvement of more than 40% at the time of staging (Morton et al., 2005, Morton et al., 2003, Morton et al., 1993). Another study evaluated an exponential increasing of lymph node metastases if the tumor becomes thicker. A thickness of 0.76 to 1.50 mm was associated with regional lymph node metastases in 2 to 25% of cases. In tumors with a thickness between 1.51 to 4.00 mm the rate of regional lymph node metastases developed to 57%. A tumor thickness larger than 4 mm was associated with microscopic presence of metastases within the lymph nodes (Balch, 1999, Balch et al., 2000, Balch et al., 1996). There has been evidence that lymph node dissection resulted in an increase of overall survival compared to patients receiving palliative treatment to the neck only (Balch, 1999, Balch et al., 2000, Balch et al., 1996, Balch et al., 1993, Cascinelli et al., 1998). Negative lymph nodes are a strong prognostic factor for survival, whereas lymph node metastases yield a 6 times higher relative risk for death (Balch et al., 2009, Gershenwald et al., 1999).  

Patients who suffered from oral mucosal malignant melanomas are often diagnosed at an advanced stage followed by ulceration, microsatellites or regional nodal metastases (Chaudhry et al., 1958, Morton et al., 1993, Mücke et al., 2009, Patel et al., 2002, Prasad et al., 2004, Rapidis et al., 2003, Temam et al., 2005). This high rate of regional lymph node metastases means that patients at risk should be considered for therapeutic elective neck dissection with a low threshold for surgery. Although no randomized trials on the treatment of the regional lymph nodes for oral mucosal malignant melanoma exist due to the rarity of this tumor, there is little doubt about this treatment approach. (Balch et al., 2009, Balch et al., 1996, Cascinelli et al., 1998, Chaudhry et al., 1958, Essner, 2003, Hauschild et al., 2003, Medina et al., 2003, Morton et al., 2003, Morton et al., 1993, Mücke et al., 2009, Patel et al., 2002, Tanaka et al., 2004, Temam et al., 2005). As the oral melanoma is very aggressive and the texture of the mucosa is different from the cutis with an earlier occurrence of lymph node metastases, there is actually no role for the sentinel lymph node technique, as the risk of micrometastases has to be excluded by standard therapeutic neck dissection (Prasad et al., 2004, Snow and van der Waal, 1986, Umeda and Shimada, 1994).  

2.6.2 Radiotherapy  
Radiotherapy has been used to control local recurrence (Balch et al., 1993, Harwood, 1983, Schmidt-Ullrich and Johnson, 1996, Storper et al., 1993). Postoperative, adjuvant radiation therapy results in a lower local recurrence rate in comparison to patients without radiotherapy treated by wide surgical resection only (Harwood, 1983). Hyperfractionated accelerated radiotherapies have appeared most useful (Harwood, 1983, Schmidt-Ullrich and Johnson, 1996, Storper et al., 1993), although the differences were not found to be statistically significant. The adjuvant performance of radiotherapy should be considered in advanced stage malignant melanomas of the oral cavity. There are still no data available from randomized trials regarding the efficacy of adjuvant radiotherapy.  

2.7 Adjuvant therapy  
Adjuvant therapy modalities vary and include the application of non-specific immunostimulants (Grooms et al., 1977, Morton et al., 1970, Morton et al., 1974, Sondak and Wolfe, 1997), specific immunostimulants (Interferons), vaccination therapy, cytotoxic chemotherapy, and target-therapy. Non-specific immunostimulants like Bacille Calmette-Guérin (BCG), Cryptosporidium parvum, Levanisole, thymosin, isoprinosine, transfer factor and retinoids, and interleukin
had been applied by local injection into the tumor (Grooms et al., 1977, Morton et al., 1970, Morton et al., 1974, Sondak and Wolfe, 1997). Although some authors reported limited evidence that survival was increased by this therapy this adjuvant therapy failed to prove an advantage in comparison with control treatment of any kind. Most studies performed were retrospective studies (Grooms et al., 1977, Morton et al., 1970, Morton et al., 1974, Sondak and Wolfe, 1997).

After non-specific immunostimulants have failed to establish an effect on overall survival or an improvement of symptoms, attention was paid to more specific immunostimulants such as Interferons. These glycoproteins showed a immunomodulatory and anti-tumoral effect, which was thought to be beneficial in melanoma patients. Expression of major histocompatibility complex molecules, enhancing of antigen presentation by dendritic cells, inhibition of angiogenesis, and a directly antiproliferative effect combined with the expression of melanoma-specific antigen and the stimulation of natural killer cells directly affecting the tumor was a promising treatment modality (Ascierto and Kirkwood, 2008, Janku and Kurzrock, 2010, Jonasch and Haluska, 2001, Jonasch et al., 2000, Kalani et al., 2008, Pfeffer et al., 1998). Unfortunately early enthusiasm has waned and this strategy is more and more critically debated (Janku and Kurzrock, 2010). The effect of interferon-α (IFN-α) has been well evaluated in different clinical trials in melanoma patients and a dose-dependent and duration-dependent effect has been found, especially in high-risk patients with the presence of lymph node metastases or thick melanoma patients (Kirkwood et al., 2001, Kirwood et al., 1996, Punt and Eggermont, 2001). In contrast, high-dose IFN-α is often associated with severe toxicity (Eggermont, 2002, Eggermont and Gore, 2002), and the outcome reported by the Southwest Oncology Group revealed no clinical benefit for patients who received adjuvant therapy. Indeed they may have done worse when compared to the patients who received no adjuvant therapy (Barth and Morton, 1995, Taylor et al., 1992).

Another adjuvant method for the therapy of melanoma patients are vaccination therapies. Based on the evidence that the immune system plays a natural role in melanoma progression in the same way that the previous treatment modalities tried to act at the same mechanism, vaccination therapy is designed to activate the host immune response to tumor-associated antigens. In the lack of information about specific tumor antigens, the tumor cell was the best source of antigens for activating the immune system (Hersey et al., 2002, Hersey et al., 1987, Sun et al., 1999). Previous methods of producing vaccines are always based on tumor cell preparations, but there is still no role for vaccination therapies in oral malignant melanomas.

The most established therapy beside surgery combined with radiotherapy remains cytotoxic chemotherapy. Multiple trials about a variety of cytotoxic drugs in adjuvant treatment have been performed but no study demonstrated benefits of adjuvant chemotherapy in melanoma patients at high risk for relapse or affecting overall survival significantly in controlled randomized trials. The mainstay of chemotherapy remains the palliative situation. The mainstays of cytotoxic chemotherapy include; dacarbazine, the nitrosoureas, the vinca alkaloids, cisplatin, paclitaxel, and bleomycin. The use of additional chemotherapeutic agents is still evolving. Single-drug therapy with dacarbazine reported an objective response in 18-22% of patients with measurable metastatic disease (Hill et al., 1979, Hill et al., 1981, Houghton et al., 2006, Houghton et al., 1996, Lee et al., 1995). Some trials describe efficacy of dacarbazine as a postsurgical adjuvant, but suggested no significant clinical benefit in the treatment of patients with high risk melanoma (Hill et al., 1979, Hill et al., 1981, Veronesi et al., 1982). Multiagent cytotoxic therapy is similarly unhelpful in the
adjuvant setting. Other trials of multiagent chemotherapy using nitrosoureas, dactinomycin and vincristine present contrary results (1983, Castel et al., 1991, McClay et al., 2000, Pawlik and Sondak, 2003, Wood et al., 1978).

3. Conclusion

The incidence of oral melanoma is very low and results of the treatment are still poor partly due to the advanced stage of tumor at presentation. No single management strategy or guideline can be considered the standard of care on the basis of current data. Within the head and neck the extent of the tumor, spread to the regional lymph nodes, systemic disease and histopathological variables have to be integrated into the disease staging and related to the patients’ co-morbidities and personal aims. Radicality of resection has to be balanced against the feasibility of reconstruction of the resected area obtaining form and function as well as the quality of life the patient requires. Treatment of oral mucosal malignant melanoma may not be entirely consistent with the treatment of cutaneous malignant melanoma. The thickness of the primary lesion, stage of regional lymph nodes, sex, age, the reaction of the lesion to treatment are important factors influencing prognosis and treatment choices of the disease. To date, due to the rarity of this tumor entity, no randomized trials exist demonstrating any optimal treatment algorithm. Multicenter studies collecting data about the treatment strategies and outcomes of patients suffering from oral malignant melanomas are necessary to identify the best treatment algorithm based on patient related clinical work. Oral melanomas are different from cutaneous melanomas and such studies would provide us a far better insight into their behaviour. The tumor thickness is a variable that most accurately determines therapy and prognoses, therefore, the extent of surgery margins should be decided based on the invasive depth of the primary lesion, the neck addressed on the basis of imaging staging but with a low threshold for intervention. Reconstruction follows conventional approaches but adjuvant therapy is currently disappointing. An increasing understanding of tumour immunology and biology has led to innovative therapies which are necessary if an effective treatment for oral malignant melanomas is to be developed in the future. The application of new or established technologies in experimental tumor models is necessary to increase the potential for such treatments (e.g. proteomics, targeted therapy, vaccination therapy), but is currently still an area of experimentation and hope rather than pragmatic clinical practice.

4. Acknowledgement

The authors would like to thank the patients who gave their pictures for this book chapter.

5. References

(1983) Randomized controlled trial of adjuvant chemoimmunotherapy with DTIC and BCG after complete excision of primary melanoma with a poor prognosis or melanoma metastases. Can Med Assoc J 128: 929-933.

Anneroth G, Carlson GO, Eneroth CM & Moberger G (1973) Primary melanoma in the oral mucous membrane. Sven Tandlak Tidskr 66: 27-37.
Ascierto PA & Kirkwood JM (2008) Adjuvant therapy of melanoma with interferon: lessons of the past decade. J Transl Med 6: 62.

Balch CM (1999) Randomized surgical trials involving elective node dissection for melanoma. Adv Surg 32: 255-270.

Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, Buzaid AC, Cochran AJ, Coit DG, Ding S, Eggermont AM, Flaherty KT, Gimotty PA, Kirkwood JM, McMasters KM, Mihm MC, Jr., Morton DL, Ross MI, Sober AJ & Sondak VK (2009) Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 27: 6199-6206.

Balch CM, Morton DL, Gershenwald JE, McMasters KM, Nieweg OE, Powell B, Ross MI, Sondak VK & Thompson JF (2009) Sentinel node biopsy and standard of care for melanoma. J Am Acad Dermatol 60: 872-875.

Balch CM, Soong S, Ross MI, Urist MM, Karakousis CP, Temple WJ, Mihm MC, Barnhill RL, Jewell WR, Wanebo HJ & Harrison R (1996) Efficacy of an elective lymph node dissection of 1 to 4 mm thick melanomas for patients 60 years of age and younger. Ann Surg 224: 255-263; discussion 263-256.

Balch CM, Soong SJ, Bartolucci AA, Urist MM, Karakousis CP, Smith TJ, Temple WJ, Ross MI, Jewell WR, Mihm MC, Barnhill RL & Wanebo HJ (2009) Long-term results of a multi-institutional randomized trial comparing prognostic factors and surgical results for intermediate thickness melanomas (1.0 to 4.0 mm). Intergroup Melanoma Surgical Trial. Ann Surg Oncol 7: 87-97.

Balch CM, Soong SJ, Bartolucci AA, Urist MM, Karakousis CP, Smith TJ, Temple WJ, Drzewiecki K, Jewell WR, Bartolucci AA, Mihm MC, Jr., Barnhill R & et al. (1993) Efficacy of 2-cm surgical margins for intermediate-thickness melanomas (1 to 4 mm). Results of a multi-institutional randomized surgical trial. Ann Surg 218: 262-267; discussion 267-269.

Barker BF, Carpenter WM, Daniels TE, Kahn MA, Leider AS, Lozada-Nur F, Lynch DP, Melrose R, Merrell P, Morton T, Peters E, Regezi JA, Richards SD, Rick GM, Rohrer MD, Slater L, Stewart JC, Tomich CE, Vickers RA, Wood NK & Young SK (1997) Oral mucosal melanomas: the WESTOP Banff workshop proceedings. Western Society of Teachers of Oral Pathology. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 83: 672-679.

Barth A & Morton DL (1995) The role of adjuvant therapy in melanoma management. Cancer 75: 726-734.

Batsakis JG (1982) The pathology of head and neck tumors: the lymphoepithelial lesion and Sjogren's syndrome, Part 16. Head Neck Surg 5: 150-163.

Blessing K, Sanders DS & Grant JJ (1998) Comparison of immunohistochemical staining of the novel antibody melan-A with S100 protein and HMB-45 in malignant melanoma and melanoma variants. Histopathology 32: 139-146.

Brandwein MS, Rothstein A, Lawson W, Bodian C & Urken ML (1997) Sinonasal melanoma. A clinicopathologic study of 25 cases and literature meta-analysis. Arch Otolaryngol Head Neck Surg 123: 290-296.

Cascinelli N, Morabito A, Santinami M, MacKie RM & Belli F (1998) Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. WHO Melanoma Programme. Lancet 351: 793-796.

Castel T, Estepe J, Vinolas N, Mascaro JM, Castro J, Vilalta A, Gratacos R, Daniels M, Palou J, Grau JJ & et al. (1991) Adjuvant treatment in stage I and II malignant melanoma:
a randomized trial between chemoimmunotherapy and immunotherapy. *Dermatologica* 183: 25-30.

Chang AE, Karch H & Menck HR (1998) The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer* 83: 1664-1678.

Chaudhry AP, Hampel A & Gorlin RJ (1958) Primary malignant melanoma of the oral cavity: a review of 105 cases. *Cancer* 11: 923-928.

Curtin JA, Busam K, Pinkel D & Bastian BC (2006) Somatic activation of KIT in distinct subtypes of melanoma. *J Clin Oncol* 24: 4340-4346.

Daley TD & Armstrong JE (2007) Oral manifestations of gastrointestinal diseases. *Can J Gastroenterol* 21: 241-244.

Eggermont AM (2002) Critical appraisal of IFN-alpha-based adjuvant therapy in stage II-III malignant melanoma. *Expert Rev Anticancer Ther* 2: 563-569.

Eggermont AM & Gore M (2002) European approach to adjuvant treatment of intermediate- and high-risk malignant melanoma. *Semin Oncol* 29: 382-388.

Enroth CM LC (1975) Mucosal malignant melanoma of the head and neck. *Acta Otolaryngol* 80: 452-458.

Essner R (2003) Surgical treatment of malignant melanoma. *Surg Clin North Am* 83: 109-156.

Gazit D & Daniels TE (1994) Oral melanocytic lesions: differences in expression of HMB-45 and S-100 antigens in round and spindle cells of malignant and benign lesions. *J Oral Pathol Med* 23: 60-64.

Gershenwald JE, Thompson W, Mansfield PF, Lee JE, Colome MI, Tseng CH, Lee JJ, Balch CM, Reintgen DS & Ross MI (1999) Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. *J Clin Oncol* 17: 976-983.

Gorsky M & Epstein JB (1998) Melanoma arising from the mucosal surfaces of the head and neck. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 86: 715-719.

Greene GW, Haynes JW, Dozier M, Blumberg JM & Bernier JL (1953) Primary malignant melanoma of the oral mucosa. *Oral Surg Oral Med Oral Pathol* 6: 1435-1443.

Grooms GA, Eilber FR & Morton DL (1977) Failure of adjuvant immunotherapy to prevent central nervous system metastases in malignant melanoma patients. *J Surg Oncol* 9: 147-153.

Guzzo M, Grandi C, Licitra L, Podrecca S, Cascinelli N & Molinari R (1993) Mucosal malignant melanoma of head and neck: forty-eight cases treated at Istituto Nazionale Tumori of Milan. *Eur J Surg Oncol* 19: 316-319.

Harter LP, Curtis JS, Ponto G & Craig PH (1992) Malignant seeding of the needle track during stereotaxic core needle breast biopsy. *Radiology* 185: 713-714.

Harwood AR (1983) Melanomas of the head and neck. *J Otolaryngol* 12: 64-69.

Hauschild A, Rosien F & Lischner S (2003) Surgical standards in the primary care of melanoma patients. *Onkologie* 26: 218-222.

Heaton KM, Sussman JJ, Gershenwald JE, Lee JE, Reintgen DS, Mansfield PF & Ross MI (1998) Surgical margins and prognostic factors in patients with thick (>4mm) primary melanoma. *Ann Surg Oncol* 5: 322-328.

Hersey P, Coates AS, McCarthy WH, Thompson JF, Sillar RW, McLeod R, Gill PG, Coventry BJ, McMullen A, Dillon H & Simes RJ (2002) Adjuvant immunotherapy of patients...
with high-risk melanoma using vaccinia viral lysates of melanoma: results of a randomized trial. *J Clin Oncol* 20: 4181-4190.

Hersey P, Edwards A, Coates A, Shaw H, McCarthy W & Milton G (1987) Evidence that treatment with vaccinia melanoma cell lysates (VMCL) may improve survival of patients with stage II melanoma. Treatment of stage II melanoma with viral lysates. *Cancer Immunol Immunol Ther* 25: 257-265.

Hicks MJ & Flaitz CM (2000) Oral mucosal melanoma: epidemiology and pathobiology. *Oral Oncol* 36: 152-169.

Hill GJ, 2nd, Metter GE, Krementz ET, Fletcher WS, Golomb FM, Ramirez G, Grage TB & Moss SE (1979) DTIC and combination therapy for melanoma. II. Escalating schedules of DTIC with BCNU, CCNU, and vincristine. *Cancer Treat Rep* 63: 1989-1992.

Hill GJ, 2nd, Moss SE, Golomb FM, Grage TB, Fletcher WS, Minton JP & Krementz ET (1981) DTIC and combination therapy for melanoma: III. DTIC (NSC 45388) Surgical Adjuvant Study COG PROTOCOL 7040. *Cancer* 47: 2556-2562.

Houghton AN, Coit DG, Daud A, Dilawari RA, Dimaio D, Gollob JA, Haas NB, Halpern A, Johnson TM, Kashi-Sabet M, Kraybill WG, Lange JR, Martini M, Ross RI, Samlowski WE, Sener SF, Tanabe KK, Thompson JA, Trisal V, Urist MM & Walker MJ (2006) Melanoma. *J Natl Compr Canc Netw* 4: 666-684.

Houghton AN, Meyers ML & Chapman PB (1996) Medical treatment of metastatic melanoma. *Surg Clin North Am* 76: 1343-1354.

Janku F & Kurzrock R (2010) Adjuvant interferon in high-risk melanoma: end of the era? *J Clin Oncol* 28: e15-16; author reply e17-18.

Jonasch E & Haluska FG (2001) Interferon in oncological practice: review of interferon biology, clinical applications, and toxicities. *Oncologist* 6: 34-55.

Jonasch E, Kumar UN, Linette GP, Hodi FS, Soffier RJ, Ryan BF, Sober AJ, Mihm MC, Tsao H, Langley RG, Cosimi BA, Gadd MA, Tanabe KK, Soubra W, Haynes HA, Barnhill R, Osteen R & Haluska FG (2000) Adjuvant high-dose interferon alfa-2b in patients with high-risk melanoma. *Cancer* 6: 139-145.

Kalani AD, Jack A, Montenegro G, Degliuomini J & Wallack MK (2008) Immunotherapy as an adjuvant therapy in the management of advanced, surgically resected, melanoma. *G Ital Dermatol Venereol* 143: 59-70.

Kawakami Y, Eliyahu S, Delgado CH, Robbins PF, Rivoltini L, Topalian SL, Miki T & Rosenberg SA (1994) Cloning of the gene coding for a shared human melanoma antigen recognized by autologous T cells infiltrating into tumor. *Proc Natl Acad Sci USA* 91: 3515-3519.

Kirkwood JM, Ibrahim JG, Sosman JA, Sondak VK, Agarwala SS, Ernstoff MS & Rao U (2001) High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. *J Clin Oncol* 19: 2370-2380.

Kirkwood JM, Strawderman MH, Ernstoff MS, Smith TJ, Borden EC & Blum RH (1996) Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. *J Clin Oncol* 14: 7-17.
Kusukawa J, Suefuji Y, Ryu F, Noguchi R, Iwamoto O & Kameyama T (2000) Dissemination of cancer cells into circulation occurs by incisional biopsy of oral squamous cell carcinoma. *J Oral Pathol Med* 29: 303-307.

Lamey PJ, Carmichael F & Scully C (1985) Oral pigmentation, Addison's disease and the results of screening for adrenocortical insufficiency. *Br Dent J* 158: 297-298.

Lee SM, Betticher DC & Thatcher N (1995) Melanoma: chemotherapy. *Br Med Bull* 51: 609-630.

Lee SP, Shimizu KT, Tran LM, Juillard G & Calcaterra TC (1994) Mucosal melanoma of the head and neck: the impact of local control on survival. *Laryngoscope* 104: 121-126.

Lengyel E, Gilde K, Remenar E & Esik O (2003) Malignant mucosal melanoma of the head and neck. *Pathol Oncol Res* 9: 7-12.

Liversedge RL (1975) Oral malignant melanoma. *Br J Oral Surg* 13: 40-55.

Lund VJ (1993) Malignant melanoma of the nasal cavity and paranasal sinuses. *Ear Nose Throat J* 72: 285-290.

McClay EF, McClay ME, Monroe L, Baron PL, Cole DJ, O’Brien PH, Metcalf JS & Maize JC (2000) The effect of tamoxifen and cisplatin on the disease-free and overall survival of patients with high risk malignant melanoma. *Br J Cancer* 83: 16-21.

Medina JE, Ferlito A, Pellitteri PK, Shaha AR, Khafif A, Devaney KO, Fisher SR, O’Brien CJ, Byers RM, Robbins KT, Pitman KT & Rinaldo A (2003) Current management of mucosal melanoma of the head and neck. *J Surg Oncol* 83: 116-122.

Meleti M, Mooi WJ, Casparie MK & van der Waal I (2007) Melanocytic nevi of the oral mucosa - no evidence of increased risk for oral malignant melanoma: an analysis of 119 cases. *Oral Oncol* 43: 976-981.

Mendenhall WM, Amdur RJ, Hinerman RW, Werning JW, Villaret DB & Mendenhall NP (2005) Head and neck mucosal melanoma. *Am J Clin Oncol* 28: 626-630.

Merchant HW, Hayes LE & Ellison LT (1976) Soft-palate pigmentation in lung disease, including cancer. *Oral Surg Oral Med Oral Pathol* 41: 726-733.

Messina JL, Glass LF, Cruse CW, Berman C, Ku NK & Reintgen DS (1999) Pathologic examination of the sentinel lymph node in malignant melanoma. *Am J Surg Pathol* 23: 686-690.

Moore ES & Martin H (1955) Melanoma of the upper respiratory tract and oral cavity. *Cancer* 8: 1167-1176.

Morton D, Eilber FR, Malmgren RA & Wood WC (1970) Immunological factors which influence response to immunotherapy in malignant melanoma. *Surgery* 68: 158-163; discussion 163-154.

Morton DL, Cochran AJ, Thompson JE, Elashoff R, Essner R, Glass EC, Mozzillo N, Nieweg OE, Roses DF, Hoekstra HJ, Karakousis CP, Reintgen DS, Coventry BJ & Wang HJ (2005) Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. *Ann Surg* 242: 302-311; discussion 311-303.

Morton DL, Eilber FR, Holmes EC, Hunt JS, Ketcham AS, Silverstein MJ & Sparks FC (1974) BCG immunotherapy of malignant melanoma: summary of a seven-year experience. *Ann Surg* 180: 635-643.

Morton DL, Hoon DS, Cochran AJ, Turner RR, Essner R, Takeuchi H, Wanek LA, Glass E, Foshag LJ, Hsueh EC, Bilchik AJ, Elashoff D & Elashoff R (2003) Lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma: therapeutic
utility and implications of nodal microanatomy and molecular staging for improving the accuracy of detection of nodal micrometastases. Ann Surg 238: 538-549; discussion 549-550.

Morton DL, Wen DR, Foshag LJ, Essner R & Cochran A (1993) Intraoperative lymphatic mapping and selective cervical lymphadenectomy for early-stage melanomas of the head and neck. J Clin Oncol 11: 1751-1756.

Mowad CM, Shrag J & Elenitsas R (1997) Oral pigmentation representing Laugier-Hunziker syndrome. Cutis 60: 37-39.

Mücke T, Hölzle F, Kesting MR, Loeffelbein DJ, Robitzky LK, Hohlweg-Majert B, Tannapfel A & Wolff KD (2009) Tumor size and depth in primary malignant melanoma in the oral cavity influences survival. J Oral Maxillofac Surg 67: 1409-1415.

Mücke T, Hölzle F, Wagenpfeil S, Wolff KD & Kesting M (2011) The role of tumor invasion into the mandible of oral squamous cell carcinoma. J Cancer Res Clin Oncol 137: 165-171.

Mücke T, Wolff KD, Wagenpfeil S, Mitchell DA & Hölzle F (2010) Immediate microsurgical reconstruction after tumor ablation predicts survival among patients with head and neck carcinoma. Ann Surg Oncol 17: 287-295.

Patel SG, Prasad ML, Escrig M, Singh B, Shaha AR, Kraus DH, Boyle JO, Huvos AG, Busam K & Shah JP (2002) Primary mucosal malignant melanoma of the head and neck. Head Neck 24: 247-257.

Pawlik TM & Sondak VK (2003) Malignant melanoma: current state of primary and adjuvant treatment. Crit Rev Oncol Hematol 45: 245-264.

Pfeffer LM, Dinarrello CA, Herberman RB, Williams BR, Borden EC, Bordens R, Walter MR, Nagabhushan TL, Trotta PP & Pestka S (1998) Biological properties of recombinant alpha-interferons: 40th anniversary of the discovery of interferons. Cancer Res 58: 2489-2499.

Prasad ML, Busam KJ, Patel SG, Hoshaw-Woodard S, Shah JP & Huvos AG (2003) Clinicopathologic differences in malignant melanoma arising in oral squamous and sinonasal respiratory mucosa of the upper aerodigestive tract. Arch Pathol Lab Med 127: 997-1002.

Prasad ML, Patel S, Hoshaw-Woodard S, Escrig M, Shah JP, Huvos AG & Busam KJ (2002) Prognostic factors for malignant melanoma of the squamous mucosa of the head and neck. Am J Surg Pathol 26: 883-892.

Prasad ML, Patel SG, Huvos AG, Shah JP & Busam KJ (2004) Primary mucosal melanoma of the head and neck: a proposal for microstaging localized, Stage I (lymph node-negative) tumors. Cancer 100: 1657-1664.

Punt CJ & Eggermont AM (2001) Adjuvant interferon-alpha for melanoma revisited: news from old and new studies. Ann Oncol 12: 1663-1666.

Rapidis AD, Apostolidis C, Vilos G & Valsamis S (2003) Primary malignant melanoma of the oral mucosa. J Oral Maxillofac Surg 61: 1132-1139.

Rapini RP, Golitz LE, Greer RO, Jr., Krekorian EA & Poulson T (1985) Primary malignant melanoma of the oral cavity. A review of 177 cases. Cancer 55: 1543-1551.

Ravid JM & Esteves JA (1960) Malignant melanoma of the nose and paranasal sinuses and juvenile melanoma of the nose. Arch Otolaryngol 72: 431-444.

Schmidt-Ullrich RK & Johnson CR (1996) Role of radiotherapy and hyperthermia in the management of malignant melanoma. Semin Surg Oncol 12: 407-415.
Snow GB & van der Waal I (1986) Mucosal melanomas of the head and neck. *Otolaryngol Clin North Am* 19: 537-547.

Sondak VK & Wolfe JA (1997) Adjuvant therapy for melanoma. *Curr Opin Oncol* 9: 189-204.

Stern SJ & Guillamondegui OM (1991) Mucosal melanoma of the head and neck. *Head Neck* 13: 22-27.

Storper IS, Lee SP, Abemayor E & Juillard G (1993) The role of radiation therapy in the treatment of head and neck cutaneous melanoma. *Am J Otolaryngol* 14: 426-431.

Sun Y, Paschen A & Schadendorf D (1999) Cell-based vaccination against melanoma--background, preliminary results, and perspective. *J Mol Med* 77: 593-608.

Tanaka N, Mimura M, Ogi K & Amagasa T (2004) Primary malignant melanoma of the oral cavity: assessment of outcome from the clinical records of 35 patients. *Int J Oral Maxillofac Surg* 33: 761-765.

Taylor CW, Chase EM, Whitehead RP, Rinehart JJ, Neidhart JA, Gonzalez R, Bunn PA & Hersh EM (1992) A Southwest Oncology Group Phase I study of the sequential combination of recombinant interferon-gamma and recombinant interleukin-2 in patients with cancer. *J Immunother* (1991) 11: 176-183.

Temam S, Mamelle G, Marandas P, Wibault P, Avril MF, Janot F, Julieron M, Schwaab G & Luboinski B (2005) Postoperative radiotherapy for primary mucosal melanoma of the head and neck. *Cancer* 103: 313-319.

Thompson LD, Wienke JA & Miettinen M (2003) Sinonasal tract and nasopharyngeal melanomas: a clinicopathologic study of 115 cases with a proposed staging system. *Am J Surg Pathol* 27: 594-611.

Umeda M & Shimada K (1994) Primary malignant melanoma of the oral cavity--its histological classification and results. *Br J Oral Maxillofac Surg* 32: 39-47.

Veronesi U, Adamus J, Aubert C, Bajetta E, Beretta G, Bonadonna G, Bufalino R, Cascinelli N, Cocconi G, Durand J, De Marsillac J, Ikonopisov RL, Kiss B, Lejeune F, MacKie R, Madej G, Mulder H, Mechl Z, Milton GW, Morabito A, Peter H, Priario J, Paul E, Rumke P, Sertoli R & Tomin R (1982) A randomized trial of adjuvant chemotherapy and immunotherapy in cutaneous melanoma. *N Engl J Med* 307: 913-916.

Veronesi U & Cascinelli N (1979) Surgical treatment of malignant melanoma of the skin. *World J Surg* 3: 279-288.

Veronesi U, Cascinelli N, Adamus J, Balch C, Bandiera D, Barchuk A, Bufalino R, Craig P, De Marsillac J, Durand JC & et al. (1988) Thin stage I primary cutaneous malignant melanoma. Comparison of excision with margins of 1 or 3 cm. *N Engl J Med* 318: 1159-1162.

Wood WC, Cosimi AB, Carey RW & Kaufman SD (1978) Randomized trial of adjuvant therapy for "high risk" primary malignant melanoma. *Surgery* 83: 677-681.
Surgery continues to be the mainstay treatment for melanoma localized to the primary tumor and/or lymph nodes. Results from randomized controlled trials indicate that sentinel node biopsy for the treatment of cutaneous melanoma of intermediate thickness has a beneficial effect on recurrence rates, and adjuvant radiotherapy to regional lymph node fields following surgical resection reduces loco-regional recurrence in patients at high risk of relapse. Isolated limb perfusion, electrochemotherapy, and photodynamic therapy continue to be evaluated for treatment of stage IV disease. However, the greatest excitement in new treatment has been with targeted therapies for genetic mutations. In particular, the promising results of partial and complete tumor response in stage IV disease from early phase trials of the B-RAF kinase inhibitors. This book provides a contemporary insight into the therapeutic treatment options for patients with metastatic melanoma and is relevant to clinicians and researchers worldwide. In addition, an update on current clinical trials for melanoma treatment has been included, and two chapters have been reserved to discuss the treatment of oral and uveal melanoma.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Thomas Mücke, Anna Borgmann, Klaus-Dietrich Wolff and David Andrew Mitchell (2011). Oral Malignant Melanoma, Treatment of Metastatic Melanoma, Ms Rachael Morton (Ed.), ISBN: 978-953-307-574-7, InTech, Available from: http://www.intechopen.com/books/treatment-of-metastatic-melanoma/oral-malignant-melanoma