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Review

Comparison of International Guidelines on Mucosal Melanoma of the Head and Neck: A Comprehensive Review of the Role of Radiation Therapy

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Abstract. *Mucosal melanomas of the head and neck are rare pathological entities that correlate with poor prognosis due to their high propensity for local failure and distant metastases. The exact role of radiation therapy in the management of mucosal melanoma patients has not yet been fully proven, even though in everyday clinical practice these patients are referred for radiotherapy, in an effort to improve locoregional control. The guidelines of various societies on the role of radiation therapy for the treatment of mucosal melanoma of the head and neck region are very limited. We reviewed and analyzed the guidelines developed in the U.S.A. (National Comprehensive Cancer Network), Canada (Cancer Care Ontario and Canadian Medical Association), Europe (European Society for Medical Oncology and European Society for Radiotherapy and Oncology) and Australia and New Zealand (Cancer Council Australia) and isolated evidence for the management of mucosal melanomas of the head and neck region with radiation therapy worldwide.*

Melanomas of the head and neck region represent an interesting challenge in modern oncology. Epidemiological studies have shown that 25% to 55% of all mucosal melanomas are located in the head and neck region and almost 72% of them are located in the nasal cavity and paranasal sinuses (1). Mucosal melanomas have a more aggressive behavior that cutaneous ones and have a greater probability to metastasize to locoregional and distant sites. Due to higher incidence of locoregional and distant recurrence, mucosal melanomas result in a higher death rate. The overall 5-year survival rate for non-metastatic mucosal melanomas of the head and neck is 20-33% whereas 5-year disease-specific survival is 32.4% (2-4).

Although surgery with wide margins remains the "gold standard" treatment option for mucosal melanomas of head and neck, in most cases complete resection is technically impossible, because of the proximity of the tumor to critical organs, such as the eyelids and nose, but also because of the patients' desire for an acceptable cosmetic result (5, 6).

Radiation therapy, chemotherapy, targeted biological therapies and immunotherapy are treatments applied to patients with inoperable disease or in an adjuvant setting. Regarding radiation therapy, there is no clear indication of the appropriate evidence and the best radiation scheme. Therefore, since conducting a clinical trial is not feasible due to the heterogeneity of clinical appearance and to the rarity of the disease, our experience is mainly based on data from small retrospective studies with considerable potential for bias (7).

In the present study, we aimed to review and analyze existing evidence on the application of radiation treatment on this rare entity.

Materials and Methods

We performed a literature search for guidelines on the treatment of malignant melanoma published up to October 2015 in English, by visiting the following sites: National Comprehensive Cancer Network, NCCN, USA (8), Cancer Care Ontario (CCO) and Canadian Medical Association (CMA), Canada (9), European Society for Medical Oncology (ESMO) (10), European Society for Radiotherapy and Oncology (ESTRO) (11), Cancer Council Australia (CCA) (12).

Only NCCN and the Cancer Council Australia have published guidelines focusing on mucosal melanoma, particularly in the head and neck region. The Canadians have published guidelines on the role of radiation therapy as an adjuvant treatment. From the European Societies, only ESMO has produced guidelines, but

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without any special reference to mucosal melanoma. In view of this disadvantage (melanoma *vs.* mucosal melanoma) we based our review mainly on the guidelines from Australia and the U.S.A., regarding the role of radiation therapy in this rare entity.

Results and Discussion

The increasing incidence of melanomas, the importance of early detection and the growing application of novel therapeutic approaches (targeted therapies) has led different scientific groups to develop guidelines [NCCN v.3.2015, Canada [Cancer Care Ontario (CCO) and Canadian Medical Association (CMA)], Europe [European Society for Medical Oncology (ESMO)] and Australia and New Zealand [Australian Cancer Network (ACN)]. On the other hand, as mucosal and cutaneous melanomas of the head and neck region are rare malignant entities, the management of patients is based on the general guidelines on melanomas, on published isolated case reports and on the results from small sample groups. Recently, two publications have focused on this disease entity (7, 13).

Treatment Guidelines

All guidelines agree that due to the rarity of mucosal melanoma, treatment guidelines are not well established and consideration should be given to referral to a unit with expertise in managing patients with head and neck melanomas. It is critical that multidisciplinary evaluation and treatment be coordinated by all teams involved in patient care before the initiation of any treatment.

Treatment of Primary Lesions

Australian and U.S.A. guidelines stress that the treatment of choice for the primary lesion is wide surgical resection, basing this recommendation on various studies performed over the last decades. More specifically, the Australian guidelines state that complete surgical excision is the fundamental surgical aim but may be difficult to achieve without a destructive or disabling procedure, making radical resection often very difficult and adjuvant therapy a necessity. The NCCN guidelines stress again that primary treatment should be surgical for stage III to IVA disease in the AJCC staging system (14). However, both Organizations state that surgery is not recommended for patients with stages IVB or IVC. For these patients, inclusion in clinical trials is advised or primary radiation therapy (with or without chemotherapy) should be offered. Although neck dissection is recommended in patients with clinically- or radiologically-positive nodes, the role of prophylactic neck dissection is poorly defined (15, 16).

Primary radiation therapy alone (as a monotherapy) has been advocated, but to date the series comparing it with surgery with or without radiotherapy show poorer local control and survival. Therefore, the use of this treatment modality remains unclear with the exception of patients with either non-operable disease or a poor performance status (7).

Adjuvant Radiotherapy

Historical data suggest that mucosal and cutaneous melanomas are radioresistant. The melanocytes radioresistance, of cutaneous origin, is due to their high ability to fix sub-lethal genetic errors. Studies have demonstrated that telomere length is the key to radioresistance. Several genes and their products are found to play a vital role in DNA repair mechanisms in melanoma cell lines in several studies published over the last 15 years. Down-regulation of CTC1, an important telomere maintenance patrol, enchased radiosensivity induced by DNA damage and telomere shortening (17). SLUG, a protein involved in DNA damage sensing and repair by regulating a cellular network, was found to increase radiosensivity when silenced in melanoma cells (18). FKBP51, an immunophilin with isomerase activity involved in apoptosis resistance and correlated with vertical growth and lesion thickness, shows reduced clonogenic potential when silenced after irradiation (19).

Down-regulation of the insulin-like growth factor, enhanced radiosensivity *in vitro*, as well as *in vivo* through reduced radiation-induced p53 accumulation, that functions as a DNA damage checkpoint (20).

Lastly, overexpression of dopachrome tautomerace, also known as tyrocinace related protein, correlates with relative levels of radioresistance through an increased activity of the ERK/MAPK pathway (21).

However, genetic aberrations implicated in the pathogenesis of mucosal melanomas of the head and neck have not yet been clearly defined. Somatic mutations in the *Kit* gene have an increased incidence in mucosal melanomas, whereas they are not frequent in cutaneous melanomas, while mutations in the *BRAF* gene, that have been shown to be elevated in cutaneous melanomas are rare in mucosal ones (22).

Furthermore, for mucosal melanomas, little prognostic importance has been found for features such as tumor thickness, level of invasion, ulceration, mitotic index or nerve involvement, which are factors associated with loco-regional recurrence and distant metastases in cutaneous melanomas (23, 24).

Target delineation and optimal dose distribution require experience in head and neck imaging, and a thorough understanding of patterns of disease spread. Standards for target definition, dose specification, fractionation (with and without concurrent chemotherapy), and normal tissue constraints are still evolving. IMRT, 3D, and 2D conformal techniques may be used where appropriate, depending on stage, tumor location, physician training/experience, and available physics support.

According to the U.S.A. Guidelines (NCCN), adjuvant radiation therapy should be considered in cases of head and neck melanomas in patients with inadequate margins. Radiation has a role in controlling nodal disease in patients at-risk. The guidelines emphasize the value of radiation in preventing nodal relapse, despite the increased late radiotherapy-related toxicity and the trend towards worse overall survival. Consideration should be given to the concurrent use of radiation with systemic therapy. Based on these data, the NCCN and CMA recommend adjuvant radiotherapy for patients with resected melanoma with high-risk nodal disease, including those with four or more involved lymph nodes, lymph nodes of ≥3 cm in size (lower threshold for cervical disease, two or more involved lymph nodes or lymph nodes of ≥2 cm) and macroscopic extranodal soft tissue extension. Adjuvant radiotherapy is also recommended for melanomas with close or positive margins after resection, where further excision is not anatomically feasible.

Adjuvant (postoperative) radiation therapy appears effective in improving local control and a recent meta-analysis has shown that postoperative radiation reduced the risk of local recurrence by 45% (13). Local recurrence is a frequent major issue that radiation oncologists are very often called to face, as the option of a re-operation is neither feasible nor beneficial for the patients' outcomes. Even thought there is no clear evidence for factors correlated with a higher risk of local recurrence, there are some assumptions that factors such as incomplete resection, multifocal tumors, implantation during surgery and lymphatic spread might play a crucial role (25, 26).

In two retrospective studies examining the benefit of adjuvant radiotherapy in patients with mucosal malignant melanoma (58 and 160 patients respectively) the incidence of loco-regional recurrence was lower in patients who had both radical resection and post-operative radiotherapy than those who underwent surgery alone (6, 27).

With regard to dose fractionation, twice-daily hyperfractionation had a lower risk of complications such as acute adverse events and late toxicity compared to the hypofractionation scheme, when the radiation was delivered to structures such as the nasal cavity and the paranasal sinuses. Hypofractionation has proven superior in some studies and achieved both better local control and prolonged overall survival compared to conventional-treatment fractionation (25, 28).

Regarding the importance of total dose in the management of head and neck mucosal melanoma, no clear association between an average dose and response rates has been demonstrated in the retrospective literature. The optimal radiation therapy dose regimen relies on the natural history of the disease, the patient's performance, the tumor's proximity to critical structures, and patients' ability to tolerate the scheme (7).

Nevertheless, the value of post-operative radiotherapy in overall survival is unclear and vague. Lund *et al*. performed a large retrospective study assessing whether surgery combined with radiotherapy offered any survival benefit over surgery alone. The authors concluded that the addition of postoperative radiotherapy did not improve survival rates (29).

The literature states that approximately 16% of patients diagnosed with malignant mucosal melanoma will experience regional lymph node metastasis. Candidate patients with a clinically and radiological negative neck who are at high risk of developing lymph node recurrence (for example mucosal melanomas of the oral cavity) might benefit from elective neck irradiation (23-25). Recent advances in radiation oncology have offered new treatment options for patients with mucosal melanomas of the head and neck region, treated in an adjuvant setting or as a single treatment modality.

Hyperthermia combined with radiotherapy is a safe, non-invasive technique, which is gaining ground in the treatment of superficial tumors such as those of malignant melanoma. It has been tested for killing malignant cells with promising results as an adjuvant treatment to radiation therapy (photons or electrons), in a multicenter trial by the European Society of Hyperthermic Oncology (30).

Proton-beam therapy should be considered for malignant mucosal melanomas located in the head and neck region, close to the eyes or the brain. In a pilot study published by Zenda *et al*., 14 patients with mucosal melanoma of the head and neck were treated with protons and no severe adverse effect occurred, leading to the conclusion that proton therapy can be safely administered for tumors proximal to critical anatomical structures (31). In another study, by Fuji *et al*., high-dose proton beam therapy was found to provide effective definitive local treatment for sinonasal melanomas, with results comparable to those of surgery (32).

Neutrons are a form of particle radiation of high linear energy transfer radiation that has been shown to improve therapeutic outcome in radioresistant malignancies such as sarcomas and melanomas. Its superiority compared to conventional photon beam radiation lies in that the total dose required to kill the same number of cancer cells is lower, and therefore requires fewer fractions. Only one published study exists, by Liao *et al*., examining the use of fast neutron radiotherapy in mucosal melanoma of the nasal cavity and paranasal sinuses at a total median dose of 19.2 nGy, suggesting that fast neutron radiotherapy can achieve results comparable to the outcomes seen in photon radiotherapy. However, 14% of the sample developed the severe late complication of osteonecrosis (33).

Carbon ion beam radiotherapy (CIBT), another form of particle radiotherapy, can be completed in a very short timeframe with minor adverse events. It combines the

Table I. *Radiation therapy techniques in use for the treatment of mucosal melanomas of head and neck.*

Radiation therapy technique	Advantages	Disadvantages
Photon or electron beams [Conformal radiation therapy, Radiation therapy combined with Hyperthermia, Stereotactic radiation therapy]	• Easy access • Long studying experience • Flexible radiation therapy schemes [total dose, fractionation] • Suitable for frail and elderly patients	• Difficult to overcome tumor radioresistance • Toxicity
Particle radiation therapy [Neutrons, protons, carbon ions]	• Greater biological effectiveness • Better dose distribution • Necessity for lower doses	• Difficult access • Toxicity

advantage of proton therapy with regard to dose distribution and the biological effect of a high-LET neutron beam. The use of carbon ion therapy was examined in 3 prospective studies where patients with unresectable mucosal melanoma of the head and neck received hypofractionated radiotherapy in 16 fractions of 3.6 Gy per fraction. Similarly, the results pointed out a potential significance of definitive CIRT in patients with locally advanced disease (34).

Table I summarizes the advantages and disadvantages of radiation therapy techniques available today for the treatment of patients with mucosal melanoma of the head and neck region.

Treatment of Metastatic Disease

The metastatic sites commonly requiring radiation therapy in melanoma are bone, brain, subcutaneous lesions, bulky lymph nodes, liver and adrenal metastases. Whilst many of these can be treated with short fractionation regimens such as 8 Gy in one fraction (bone metastases), 18 or 20 Gy in five fractions (brain metastases), larger and bulky tumors such as those involving lymph nodes or widespread cutaneous deposits may require more lengthy schedules, such as 40 Gy in fifteen fractions or 45 Gy in twenty fractions (35).

Special reference is made to the issue of brain metastases. Patients with multiple brain metastases are considered for whole brain irradiation, again with short (five fractions in one week) or long schemes (20 fractions in four weeks). The patients' general condition, their ability to travel to the Radiation Unit and life expectancy are the main parameters to bear in mind for choosing the appropriate scheme. For patients with one (and up to five) lesions, stereotactic radiosurgery or radiotherapy is indicated. For patients who have brain metastasis with favorable prognostic signs, including the presence of a single brain metastasis, no extracranial disease, good performance status (PS) and initial presentation with brain metastasis, resection seems to be better than WBRT. Median survival ranges from 1.8 months to 10.5 months, depending on prognostic factors. Patients with multiple surgically accessible lesions and little or no extracranial disease may also have improved prognosis when treated with resection. For patients with surgically inaccessible or multiple metastases and medical comorbidities, SRS (stereotactic radio surgery) may offer better survival than WBRT. Complete or partial response occurs in 55% of patients and freedom from progression is achieved in 90–95% after SRS. Median survival was better for a solitary lesion than multiple metastases. After surgery or SRS, adjuvant WBRT could improve local control but offers no clear survival benefit. For poor-prognosis patients, options include WBRT, chemotherapy, steroids or best supportive care. In one study, WBRT alone led to a median survival of 3.4 months compared to 2.1 months for BSC alone. Steroids given 2-7 days prior to and/or during radiation therapy improved symptoms in 73% of patients (36-38).

The role of combined radio-chemo-therapy in the management of patients with mucosal melanoma of the head and neck region is mainly explored in small phase II trials. Two small phase II studies examined the role of radiotherapy concurrent with chemotherapy using temozolomide and fotemustine with MS of 8 months. Avril *et al*. reported an RR of 5.9% for fotemustine, compared with DTIC in a phase III trial of metastatic melanomas, where 18% of patients had brain metastases. Problems with phase II studies were illustrated by an Avril *et al*. study in which the previously reported phase II response rate of nearly 30% was not replicated in this larger phase III study (39, 40).

Conclusion

Although rare, malignant mucosal melanomas of the head and neck region represent a difficult challenge, because their optimal management is not based on a clear consensus. Radiation therapy is a treatment modality that should be offered to patients with non-resectable disease, where the risk of loco-regional recurrence is high or there is symptomatic metastatic disease. All specialties involved in

the management of melanomas should consider radiation as an additional weapon in the fight against this aggressive malignancy. More studies are required, as there is still no consensus on the optimal radiation doses and fractionation.

Conflicts of Interest

None.

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