

# Head and Neck Mucosal Melanoma

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**Purpose:** The purpose of this article is to discuss the optimal treatment and outcomes for head and neck mucosal melanoma.

**Methods:** Review the pertinent literature.

**Results:** Head and neck mucosal melanoma is a rare entity comprising less than 1% for all Western melanomas. It usually arises in the nasal cavity, paranasal sinuses, and oral cavity. The optimal treatment is surgery. The likelihood of local recurrence after resection is approximately 50%. Radiotherapy (RT) reduces the likelihood of local failure but probably does not enhance survival, which is primarily impacted by advanced T stage and the presence of regional metastases. The 5-year survival rates vary from approximately 20 to 50%. Although the median time to relapse is roughly 1 year or less, late failures are common and cause-specific survival continues to decline after 5 years.

**Conclusion:** The optimal treatment is surgery. Postoperative RT improves local-regional control but may not impact survival. Definitive RT may occasionally cure patients with unresectable local-regional disease or at least provide long-term palliation.

**Key Words:** mucosal melanoma, radiotherapy, treatment, outcomes

(*Am J Clin Oncol* 2005;28: 626–630)

Head and neck mucosal melanoma is a rare entity comprising less than 1% of all melanomas in the West and less than 10% of head and neck melanomas.<sup>1–3</sup> Andersen et al<sup>2</sup> reviewed 2.5 million individuals in Denmark over a 30-year period and found that head and neck mucosal melanomas accounted for 0.8% of all melanomas and 8% of head and neck melanomas. Chang et al<sup>1</sup> reported 84,836 patients from the United States Cancer Registry from 1985 to 1994; 611 patients (0.7%) had head and neck mucosal melanomas. Ethnicity significantly influences the prevalence of head and neck mucosal melanomas. Although it accounts for less than 1% of all Western melanomas, it comprises one fourth to one third of melanomas found in Japan.<sup>4,5</sup>

The median age of patients with head and neck mucosal melanoma is approximately 60 years, with a wide range varying from roughly 20 years to more than 90 years (Table 1). There is a modest male preponderance (Table 1). The most common primary sites include the nasal cavity, paranasal sinuses, and oral cavity (Table 1). Within these sites, the nasal cavity, maxillary alveolar ridge, and hard palate are most often involved.<sup>3,6,7</sup>

The majority of patients present with disease confined to the primary site (stage I), 10 to 30% have clinically positive cervical adenopathy at diagnosis (stage II), and 15% or less present with hematogenous dissemination (stage III; Table 1). The likelihood of presenting with regional metastases varies with primary site. Temam et al<sup>8</sup> reported 69 patients treated at the Institut Gustave-Roussy (Villejuif, France). Clinically positive regional adenopathy was observed in 5 of 46 patients (11%) with sinonasal melanomas compared with 11 of 23 patients (47%) with melanomas arising in the oral cavity or pharyngolarynx.<sup>8</sup> Distant metastases may be found in a variety of sites, including the lungs, bones, liver, brain, and skin.<sup>8</sup>

## HISTOPATHOLOGY

The histologic appearance of head and neck mucosal melanoma is variable. The tumor cells may be plasmacytoid, sarcomatoid (spindle cells), or epithelioid.<sup>4</sup> Melanin content may also vary from heavily pigmented tumors to those that are amelanotic.<sup>4</sup> Desmoplastic melanoma, first described by Conley in 1971, rarely arises in head and neck mucosal sites.<sup>9,10</sup> They are comprised of amelanotic, poorly circumscribed fascicles and bundles of spindle cells with hyperchromatic nuclei associated with a dense fibrous stroma and may be confused with other neoplasms, including fibrosarcoma, malignant peripheral nerve sheath tumors, and spindle cell carcinomas.<sup>5,10,11</sup> Desmoplastic mucosal melanomas often exhibit perineural invasion and aberrant p53 expression.<sup>9</sup> The prognosis of patients with this rare variant is probably similar to that of patients with more pedestrian variants of head and neck mucosal melanoma.<sup>10,11</sup>

Immunohistochemical stains may help distinguish mucosal melanomas from other malignancies. They are likely to stain positively for S-100, vimentin, and HMB-45, and negatively for cytokeratin and epithelial membrane antigen.<sup>4</sup> Brandwein et al<sup>4</sup> reported the following positive immunohistochemical staining patterns in a series of patients treated at the Mount Sinai Medical Center (New York, USA): S-100,

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ISSN: 0277-3732/05/2806-0626

DOI: 10.1097/01.coc.0000170805.14058.d3

**TABLE 1.** Demographic Parameters

Parameter	Series				
	MSKCC <sup>17</sup>	IGR <sup>8</sup>	INT <sup>16</sup>	MDAH <sup>15</sup>	RMH <sup>19</sup>
No. patients	59	69	48	42	89
Age, y	Median, 63; range, 23–93	Mean, 59; range, 21–90	Mean, 58; range, 21–79	Median, 60; range, 23–89	Median, 64; range, 25–94
Male-to-female ratio	1.4:1	1.1:1	2.4:1	1.2:1	1:1.1
Site					
Sinonasal	59%	67%	54%	55%	79%
Oral cavity	41%	27%	32%	45%	21%*
Other	0%	6%	14%	0%	0%
Stage					
I	80%	77%	60%	74%	85%
II	13%	23%	32%	12%	8%
III	7%	0%	8%	14%	7%

\*Oral cavity and oropharynx.

IGR, Institut Gustave-Roussy; INT, Istituto Nazionale Tumori; MDAH, M.D. Anderson Hospital; MSKCC, Memorial Sloan Kettering Cancer Center; RMH, Royal Marsden Hospital.

14 of 14 (100%); HMB-45, 12 of 14 (86%); vimentin, 9 of 10 (90%); and cytokeratin, 0 of 9 (0%).

### DIAGNOSTIC EVALUATION

A complete history is obtained and a thorough head and neck examination is performed, including fiberoptic nasopharyngoscopy. Computed tomography (CT) is used to evaluate the primary tumor and cervical lymph nodes. Magnetic resonance imaging (MRI) is useful to evaluate the extent of sinonasal tumors, particularly for those that may involve the skull base and/or exhibit neurotropic spread. A chest radiograph is used to detect pulmonary metastases. Depending on the patient's presenting symptoms, additional studies may be indicated to detect distant metastases including brain MRI, chest CT, bone scan, and/or position emission tomography.<sup>12,13</sup>

### STAGING

Patients may be staged according to the American Joint Committee on Cancer<sup>14</sup> staging system. Alternatively, tumors may be stratified as follows: stage I, confined to the primary site; stage II, positive cervical lymph nodes; and stage III, distant metastases.<sup>6,8,15–17</sup>

Depth of invasion within stage I tumors may be useful to predict outcome.<sup>11</sup> Prasad et al<sup>11</sup> reported 61 patients with stage I head and neck mucosal melanomas treated at the Memorial Sloan Kettering Cancer Center (New York) between 1956 and 2000. The tumors were stratified as follows: level 1, melanoma in situ or microinvasion (4 patients); level 2, invasion to the lamina propria (29 patients); and level 3, deep invasion into skeletal muscle, cartilage, and/or bone (28 patients). Patients were treated with surgery alone or combined with radiotherapy (RT) and had follow-up for 1 to 198 months (median, 20 months). The 5-year cause-specific survival rate was 43%. The following parameters were evaluated

in a multivariate analysis of cause-specific survival: primary site (sinonasal vs oral cavity), tumor thickness, vascular invasion, tumor necrosis, cell morphology (differentiated vs undifferentiated), architecture (pseudo papillary or sarcomatoid vs other), and level of invasion. The only parameter that significantly influenced cause-specific survival was level of invasion ( $P = 0.03$ ).

### TREATMENT

The mainstay of treatment of patients with head and neck mucosal melanomas is surgery, which entails complete resection of the primary tumor and any positive cervical lymph nodes. Postoperative RT should be considered to reduce the likelihood of local–regional recurrence. Management of the clinically negative neck is controversial.<sup>18</sup> However, because of the relatively high risk of regional metastases, our bias is to treat the neck electively, particularly for patients with oral cavity and pharyngolaryngeal tumors.

Patients with unresectable, locally advanced disease may be treated with definitive RT that will often result in long-term palliation and, sometimes, cure. Although it is uncommon to treat resectable head and neck mucosal melanomas with this modality in the United States, it is within the standard of care in some centers.<sup>18</sup>

The efficacy of adjuvant systemic therapy, such as interferon and vaccine therapy, remains investigational for patients with unfavorable cutaneous melanomas. Because of the rarity of head and neck mucosal melanomas, it is unlikely that studies investigating adjuvant systemic therapy for this disease will be forthcoming. Therefore, it is reasonable to extrapolate data from studies evaluating this form of therapy in patients with cutaneous melanomas.

## OUTCOMES

It is difficult to compare the outcomes after different treatment approaches because of the rarity of the disease, variability of treatment strategies within a single institution, and inclusion of patients with disseminated disease (Table 2). Most of the outcome studies in the literature report the efficacy of surgery alone or combined with adjuvant RT. The relatively small proportion of patients with unresectable or disseminated disease are more likely to receive RT alone and/or systemic chemotherapy or immunotherapy and, predictably, fare poorly. A small number of studies report the efficacy of definitive RT. Therefore, outcomes data are presented as either primarily surgical or definitive RT.

### SURGERY ALONE OR COMBINED WITH ADJUVANT RADIOTHERAPY

Outcomes after surgery alone or combined with adjuvant RT and/or systemic therapy are presented in Table 2. The proportion of patients who received surgery as part of their treatment is indicated. The local control rates vary from approximately 40 to 60% at 5 years. Although the majority of recurrences are observed within 1 to 2 years after treatment, late recurrences are seen after 5 years, and the cause-specific survival rates continue to decline with further follow-up. A number of parameters have been investigated to determine their potential impact on local control and survival. Patel et al<sup>17</sup> performed a multivariate analysis of local control in a series of 59 patients treated at the Memorial Sloan Kettering Cancer Center and found that only vascular invasion ( $P = 0.0001$ ) significantly influenced this end point. Multivariate analysis of cause-specific survival revealed that it was significantly adversely influenced by advanced clinical stage,

primary tumor thickness more than 5 mm, presence of vascular invasion, and the development of distant metastases.<sup>17</sup>

Temam et al<sup>8</sup> reported 69 patients treated at the Institut Gustave-Roussy between 1979 and 1997 with either surgery alone (30 patients) or combined with postoperative RT (39 patients). Patients who received postoperative RT were more likely to have T3–T4 tumors (44% vs 17%) and positive cervical nodes (33% vs 13%) compared with those treated with surgery alone. Patients had follow-up from 8 to 384 months (median, 3.8 years). Local control rates were as follows: surgery alone, 8 of 30 patients (26%); surgery and postoperative RT, 24 of 39 patients (62%); and overall, 32 of 69 patients (46%). Multivariate analysis of local control revealed that the use of postoperative RT was significantly associated with an improvement of this end point ( $P = 0.05$ ). However, multivariate analysis of overall survival revealed that only advanced T stage adversely impacted this end point ( $P = 0.003$ ). Pathologic neck stage and the use of postoperative RT did not significantly influence the probability of overall survival.

Yii et al<sup>19</sup> reported 89 patients treated at the Royal Marsden Hospital (London, UK) between 1945 and 1996. Stage distribution at presentation was as follows: stage I, 76 patients (85%); stage II, 7 patients (8%); and stage III, 6 patients (7%). Surgery alone or combined with RT and/or systemic therapy was used in 68 patients (76%). Seventy-five of 76 patients with stage I melanomas received some form of treatment. Fifty-four of 75 patients (72%) developed a local recurrence, 18 patients (24%) failed in the neck, and 30 patients (40%) developed distant metastases. The 5-year survival rates were stage I, 26%; stages II and III, (0%); and overall, 23%. Survival decreased to 12% at 10 years.

**TABLE 2.** Treatment Outcomes\*

Parameter	Series			
	MSKCC <sup>17</sup>	IGR <sup>8</sup>	INT <sup>16</sup>	MDAH <sup>15</sup>
No. of patients	59	69	48	42
Follow-up, y	—	Median, 3.8; range, 0.7–32	—	Median, 3 —
Stage				
I	80%	77%	60%	74%
II	13%	23%	32%	12%
III	7%	0%	8%	14%
Proportion treated surgically	100%	100%	90%	79%
Local control	~40% (5y)	46%	—	60%
Regional control	71%	77%	—	83%
DMFS	49%	32%	—	36%
CSS	44% (5y)	—	—	—
DFS	—	—	7% (4y)	40% (5y)
OS	35% (5y)	20% (5y)	21% (5y)	48% (5y)

\*Outcomes are crude percentages unless accompanied by a time interval (in parentheses).

CSS, cause-specific survival; DFS, disease-free survival; DMFS, distant metastasis-free survival; IGR, Institut Gustave-Roussy; INT, Istituto Nazionale Tumori; MDAH, M.D. Anderson Hospital; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival.

Owens et al<sup>20</sup> reported an update of the M.D. Anderson Hospital experience and analyzed 44 patients treated with surgery alone (20 patients) or combined with postoperative RT (24 patients) between 1985 and 1998. Nine of 20 patients (45%) treated with surgery alone developed a local–regional recurrence compared with 4 of 24 patients (17%) who received postoperative RT. Distant metastases were observed in 10 of 20 patients (50%) treated with surgery alone compared with 11 of 24 patients (46%) who received surgery and postoperative RT. The 5-year survival rate was 45% after surgery alone and 29% after surgery and postoperative RT. Although adjuvant RT improved the likelihood of local–regional control, the lack of improvement in survival was attributed to the high risk of hematogenous dissemination.

### DEFINITIVE RADIOTHERAPY

Stern and Guillaumondegui<sup>15</sup> reported that 5 of 42 patients treated at M.D. Anderson Cancer Center received definitive RT; 2 of 5 remained alive and disease-free at 5 years after treatment. Harwood and Cummings<sup>21</sup> reported 12 patients treated with definitive RT at the Princess Margaret Hospital (Toronto, Canada) between 1958 and 1980. Local control was observed in 6 of 12 patients at 6 months to 4.25 years after RT. Four of 12 patients remained alive and disease free from 6 months to 3.5 years after treatment, and 1 patient died of intercurrent disease at 4.25 years.

Gilligan and Slevin<sup>18</sup> reported 28 patients with sinonasal mucosal melanomas treated with definitive RT between 1961 and 1985 at the Christie Hospital (Manchester, UK). Most patients received 50 to 55 Gy in 15 to 16 fractions over 20 to 21 days. Seventeen of 28 patients (61%) were locally controlled after RT. Three patients who developed a local recurrence underwent salvage surgery, and 1 was successfully salvaged for an ultimate local control rate of 64%. Eight of 28 patients (29%) developed cervical metastases and all died with disease. Five of 28 patients (18%) survived 5 years.

Shibuya et al<sup>22</sup> reported 28 Japanese patients treated at the Tokyo Medical and Dental University (Japan) between 1963 and 1988 for melanoma of the maxillary alveolar ridge and hard palate. Twenty-five patients received definitive RT, 2 patients received preoperative RT and surgery, and 1 patient received palliative RT. Ten patients (36%) presented with clinically positive cervical nodes and 9 patients (32%) subsequently failed in the neck. Sixteen of 19 patients (84%) with positive nodes, at some point in their disease process, developed distant metastases. Local control was obtained in 14 of 18 patients (78%) with stage I tumors compared with 8 of 10 patients (80%) with stage II malignancies. The latter subset of patients had a relatively short follow-up because of the development of distant metastases. Fourteen of 28 patients (50%) were alive at 5 years, and 8 of 28 patients (29%) were disease free at 3 years.

Wada et al<sup>23</sup> reported 31 patients with localized head and neck mucosal melanoma treated with RT at 9 institutions in northern Japan between 1980 and 1999. Twenty-one patients received RT alone and 10 patients were treated postoperatively for gross residual tumor. Total dose ranged from

32 to 64 Gy (median, 50 Gy) at 1.5 to 13.8 Gy per fraction. Patients had follow-up from 1 to 214 months (median, 16 months). Three-year outcomes were local control, 30%; distant metastasis-free survival, 56%; and cause-specific survival, 33%. Five of 31 patients (16%) failed out of field in the cervical lymph nodes.

### CONCLUSION

The preferred treatment of head and neck mucosal melanoma is surgery. Postoperative RT should be considered in most cases because of the high risk of local recurrence after an apparent complete resection, even for patients with relatively localized tumors. Elective treatment of the clinically negative neck with either an elective neck dissection or RT should be used because of the high risk of subclinical disease, particularly in patients with oral cavity and pharyngolaryngeal tumors. Although patients with positive neck nodes are likely to develop distant metastases, patients who obtain local–regional control after treatment may be more likely to survive long term.<sup>6,17</sup> Although definitive RT may cure a significant subset of patients and result in similar 5-year survival rates compared with surgery, it is likely that local–regional control is better after combined surgery and adjuvant RT. Additionally, patients treated with definitive RT may be at a higher risk of late complications such as osteoradionecrosis and damage to the visual apparatus. The risk of radiation-induced optic neuropathy and/or retinopathy is probably lower after lower doses of postoperative RT compared with higher dose definitive RT.<sup>24,25</sup> Twice-daily RT may further reduce the risk of visual complications for patients with sinonasal melanomas.<sup>24,25</sup> The use of heavy-particle RT, such as protons or carbon ions, may be used to produce a more conformal dose distribution that may further enhance the therapeutic ratio and reduce the risk of severe late complications for patients with sinonasal melanomas.

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