

Survival in Sinonasal Melanoma: A Meta-analysis

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J Neurol Surg B 2012;73:157–162.

Abstract

Sinonasal melanoma is an uncommon tumor which carries a poor prognosis and high rates of local and regional recurrence and distant metastasis. While surgical resection is the mainstay of treatment, the utility of multimodality therapy has not been well studied or established. We sought to better evaluate the optimal treatment modality for sinonasal melanoma. We reviewed 39 case reports involving 423 patients with sinonasal melanoma and present a meta-analysis comparing survival by treatment modality. The two-tailed *p*-value for survival by treatment modality was determined. The number of primary site/local, regional, and distant recurrences was determined where data was available. There was a nonsignificant increase in survival for patients treated with surgery + radiotherapy versus surgery alone. There was a statistically significant increase in survival for surgery + chemotherapy versus chemotherapy alone and versus surgery alone. Patients treated with combined surgery, radiation, and chemotherapy had a statistically shorter survival interval than patients treated with surgery + chemotherapy, which may reflect more advanced disease in patients treated with triple therapy. There was no statistically significant increase in survival found for the addition of radiation to surgery. This meta-analysis demonstrates that multimodality therapy, particularly the addition of chemo-or immunotherapy to surgery, may increase survival in a subset of patients. Radiation therapy did not appear to increase survival. There may be a significant increase in overall survival with combined modality therapy with surgery and chemo/immunotherapy versus single modality therapy. Level of evidence: III. Grade of recommendation: C.

Keywords

- ▶ sinonasal
- ▶ melanoma
- ▶ skull base
- ▶ endoscopic

Mucosal melanoma of the head and neck accounts for only 25 to 30% of total melanomas with sinonasal melanoma accounting for less than 5% of these. Sinonasal melanoma carries a relatively poor prognosis, owing to the tendency of sinonasal melanoma to present at an advanced stage. A standardized treatment regimen has been difficult to develop, owing to the low incidence of the disease. Typically sinonasal melanoma has been thought to be a radiation-resistant disease, and thus surgical resection with clear margins has been the key component of therapy with curative intent, while chemotherapy and immunotherapy have

typically been reserved for unresectable or metastatic disease. Recent literature has suggested, however, that there may be a 50 to 75% initial response rate when radiotherapy alone is used.¹ It has not been shown definitively that there is a survival advantage with the addition of radio- or chemotherapy to surgery. One of our primary aims was to determine whether there is a statistically significant increase in survival with combined therapy versus single modality therapy. In addition, we sought to characterize the most frequent primary site location, as well as the frequency of metastasis to the neck.

received

July 9, 2011

accepted

October 18, 2011

published online

February 22, 2012

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Tel: +1(212) 584-4662.

DOI <http://dx.doi.org/10.1055/s-0032-1301400>.
ISSN 2193-6331.

Table 1 Average Survival (Months) by Treatment Modality

| Modality | n | Average Survival (Months) | Standard Deviation |
|---------------------------------------|----|---------------------------|--------------------|
| Surgery | 53 | 24.15 | 19.78 |
| Surgery + Radiotherapy | 91 | 30.12 | 29.27 |
| Surgery + Radiotherapy + Chemotherapy | 26 | 23.45 | 24.56 |
| Radiotherapy | 15 | 18.73 | 17.66 |
| Chemotherapy | 3 | 12.7 | 5.8 |
| Surgery + Chemotherapy | 15 | 38.8 | 17.1 |
| Chemotherapy + Radiotherapy | 3 | 38.7 | 40.3 |

Methods

Average survival was calculated as the average of the longest survival reported for each patient in each treatment group. Chemotherapy and immunotherapy were grouped together in the chemotherapy group. Two-sided *p*-values for survival were calculated using the Student's *t*-test with values <0.05 considered significant.

Results

Thirty-nine reviews, case series, and case reports were studied totaling 423 patients with sinonasal melanoma.²⁻⁴⁰ Of the 206 patients for whom treatment and survival data was provided, 53 patients were treated with surgery alone, while 91 were treated with surgery and radiotherapy and 26 patients were treated with surgery along with chemoradiation. Fifteen patients were treated with radiotherapy alone whereas 3 patients were treated with chemotherapy alone, 15 patients were treated with surgery plus chemotherapy, and 3 patients were treated with chemoradiation. ► **Table 1** shows average survival by treatment modality, whereas ► **Table 2** shows *p*-values for comparisons between

treatment modalities. The average survival was 24.15 months for surgery alone, 30.12 months for surgery and radiotherapy, and 23.45 months for surgery and chemoradiation. The two-tailed *p*-value was not significant for any of these differences in survival. The average survival for radiotherapy, chemotherapy, surgery + chemotherapy, and chemoradiotherapy was 18.73, 12.67, 38.83, and 38.67 months respectively. Of these, the increases in survival interval between surgery + chemotherapy and both chemotherapy alone and surgery alone were statistically significant, with *p*-values of 0.0205 and 0.0112, respectively. There was also a statistically significant decrease in survival for patients treated with surgery, radiation, and chemotherapy versus patients treated with surgery and chemotherapy, with a *p*-value of 0.0387.

Of the 423 patients, there were 17 patients specifically reported to have metastases to the neck, but 36 reported regional metastases. Two hundred and six recurrences were reported, for a recurrence rate of 54.6%. The most common primary site was the nasal cavity/nasopharynx with 165 cases. Unspecified sinus was next most frequent with 54 cases, followed by turbinate unspecified with 34 and the nasal septum with 33 cases.

Table 2 Two-Tailed *p*-Value by Treatment Modality

| Modality | Two-Tailed <i>p</i> -Value for Overall Survival |
|----------------------------------------------------------------------|-------------------------------------------------|
| Surgery survival vs. surgery + radiotherapy survival | 0.1895 |
| Surgery survival vs. triple therapy survival | 0.8925 |
| Surgery + radiotherapy survival vs. triple therapy survival | 0.2921 |
| Surgery survival vs. radiotherapy survival | 0.3421 |
| Surgery + radiotherapy survival vs. radiotherapy survival | 0.1474 |
| Triple therapy survival vs. radiotherapy survival | 0.5182 |
| Chemotherapy + radiotherapy survival vs. chemotherapy alone survival | 0.3305 |
| Surgery + chemotherapy survival vs. chemotherapy alone survival | 0.0205 ^a |
| Surgery survival vs. chemotherapy survival | 0.3242 |
| Triple therapy survival vs. chemotherapy survival | 0.4615 |
| Surgery + chemotherapy survival vs. surgery alone survival | 0.0112 ^a |
| Triple therapy survival vs. surgery + chemotherapy survival | 0.0387 ^a |
| Chemotherapy + surgery vs. chemotherapy + radiation survival | 0.9907 |

^aStatistically significant.

Discussion

The question of whether to add radiation and chemotherapy to surgery in treatment of nasal melanoma has been a difficult question to answer. Given the low incidence of melanoma of the sinonasal cavity it is difficult to assemble randomized control trials or even large case-control studies. Sinonasal melanoma has been thought to be a radioresistant disease, with surgery with negative margins being the primary modality for attempted cure. We sought to elucidate whether combined therapy increased survival in primary sinonasal melanoma over single modality therapy. We performed a meta-analysis of 423 patients with histologically confirmed sinonasal melanoma. The majority of patients (135/206) for whom data on treatment modality was provided were treated with some form of combined modality therapy. The majority were treated with surgery + radiation or surgery alone. No significant difference was seen between surgery or combined surgery + radiation. Interestingly, survival was actually decreased for patients treated with surgery, radiation, and chemotherapy, although this difference was nonsignificant versus surgery + chemotherapy (23.45 months vs. 38.83 months, $p = 0.0387$). This may reflect a higher stage of disease in patients treated with triple therapy. This hypothesis is difficult to confirm as only two studies reported the specific stage for patients in these two treatment groups, with three patients in both the triple therapy and surgery + chemotherapy group noted to have metastatic disease and no specific data on stage available for the remainder of the patients in these two treatment groups. As might be expected, the shortest survival was found for chemotherapy alone at 12.7 months. This difference was not significant for chemotherapy alone versus surgery alone or radiation alone. There was, however, a statistically significant ($p = 0.0205$) increase in survival for surgical treatment + chemotherapy (38.82 ± 17.05 months) versus chemotherapy alone (12.7 ± 5.8 months). There was also a statistically significant increase in survival for surgery + chemotherapy versus surgery alone (24.15 ± 19.78 , p -value = 0.0112). Other than the statistically significant increase in survival for surgery + chemotherapy versus chemotherapy alone and surgery alone, and the decreased survival in patients treated with triple modality therapy versus surgery + chemotherapy, no significant increase in survival was seen for any other single- or multimodality therapy. This is consistent with previous data showing that radiotherapy adds little to overall survival in sinonasal melanoma.

The vast majority of primary sinonasal melanomas occurred in the nasal cavity or nasopharynx. The most common sinus primaries were maxillary and ethmoid, with primary sphenoid sinonasal melanoma being quite rare, with only five cases seen. Average survival for all modalities was 27.41 ± 24.32 months. This number is consistent with other studies showing an average survival of ~ 2 years.⁴¹

Distant metastases were by far the most common site of recurrence (90, 44%), with locoregional (45, 22%), regional (36, 17%), and local (35, 17%) recurrence much less prevalent

than distant metastases. The rate of regional metastasis in this meta-analysis is consistent with the 5 to 25% range found in most series. Given this relatively low rate in sinonasal melanoma, elective neck dissection has not been widely advocated, in contrast to oral cavity mucosal melanoma, which carries a much higher rate of nodal metastasis.^{10,42}

This seems to indicate that even with good local or regional control, sinonasal melanoma is difficult to control as distant spread is likely to occur even in the presence of good locoregional control. This is consistent with other reports^{41,43} indicating that even after extensive surgical resection, local control has been reported to be below 50%, and that distant and regional metastases are relatively common, occurring in 25% or more patients in most series.^{41,43} This may at least partially explain the lack of survival benefit with combined modality therapy versus single modality therapy. The propensity for recurrence is so high that significant improvements in local or locoregional control with combined therapy are likely lost due to the high frequency of recurrence, particular of distant recurrence/metastasis.

Ninety percent of the patients in this meta-analysis (185/206 patients) for whom treatment data was reported received some form of surgical therapy. Our data and previous reports indicate that while surgery is the primary modality for treatment of sinonasal melanoma, survival remains poor even in patients with gross local control, likely secondary to both the high rate of distant metastases (44% in our data) along with the high rate of microscopic disease.⁴³ Patients with positive surgical margins have a greatly increased risk of dying from mucosal melanoma, and lack of local control has been shown to increase the rate of distant metastases.⁴⁴ The poor survival in sinonasal melanoma even with aggressive surgical management in the vast majority of patients may result from the presence of microscopic disease as well as occult distant metastases.

Fifteen of 206 patients (7%) were treated with radiotherapy alone, while 91 of 206 (44%) were treated with adjuvant radiotherapy with surgery, and 26/206 (13%) with triple therapy and 3/206 (0.01%) with chemoradiation. Adjuvant radiotherapy has become widely used in sinonasal melanoma, despite the lack of clear evidence of a survival benefit. Temam et al⁴⁵ found that while adjuvant radiotherapy produced a statistically significant increase in local control in head and neck melanoma, the rate of distant metastasis and disease-free survival was not affected in a statistically significant fashion. Krengli et al⁴⁶ and Owens et al⁴⁷ found similar results, with radiation improving local and locoregional control, but not affecting overall survival. We similarly found no statistically significant increase in overall survival for the addition of radiation to any other modality, or as primary therapy. Sufficient data was not available on our meta-analysis population to examine the effect of either adjuvant or primary radiation on local or locoregional control. Owens et al felt that the lack of improvement in overall survival with either primary radiation or adjuvant radiotherapy was due to the high rate of metastatic disease in these series. This seems to be a likely explanation, as in our meta-analysis we noted that the majority of recurrences (90) were distant

recurrences, which is consistent with the high rate of metastasis seen in these prior studies.

In our meta-analysis 3 of 206 patients (0.01%) were treated with chemotherapy or immunotherapy alone, 3 of 206 (0.01%) with chemotherapy with radiotherapy, 15/206 with surgery + chemotherapy (0.07%), and 26/206 (0.12%) with triple therapy. We observed a statistically significant increase in survival for surgery + chemotherapy versus both chemotherapy alone and surgery alone. We also noted a statistically significant decrease in survival for patients treated with triple therapy versus surgery + chemotherapy only. Due to the lack of specific data given on the immunotherapy or chemotherapy regimen given on each patient, we grouped chemotherapy and bio- or immunotherapy together. There is no standardized systemic therapy for sinonasal melanoma, and many patients are treated with a chemotherapeutic agent in conjunction with a biologic or immunotherapeutic agent such as Bacillus Calmette-Guérin, interferon- α , or interleukin-2. Ives et al examined the effectiveness of chemotherapy versus immunotherapy in patients with metastatic cutaneous melanoma.⁴⁸ They specifically examined the effect of adding interferon- α (IFN) \pm interleukin-2 (IL-2) to chemotherapy in patients with metastatic melanoma. Their meta-analysis of trials of biochemotherapy versus chemotherapy evaluated rates of partial response, complete response and overall (partial + complete) response; response duration; progression-free survival, overall survival, and toxicity. A subgroup analysis was performed by type of immunotherapy, according to whether IFN only or IFN and IL-2 were administered in the biochemotherapy arm. They found a clear benefit for biochemotherapy for partial, complete, and overall response for both the IFN and IFN + IL-2 groups. They found no benefit in overall survival for biochemotherapy versus chemotherapy. There was a significant heterogeneity in the types of chemotherapy utilized. Most trials used a single-agent chemotherapy regimen, DTIC, temozolomide, or vindesine. One trial used combination aranoza and cisplatin. The trials of chemotherapy \pm IFN and IL-2 used combination DTIC and cisplatin or a triple chemotherapy regimen of DTIC and cisplatin combined with carmustine, vinblastine, or vindesine. The studies included in our meta-analysis did not provide consistent data on the specific regimen used.

Data on chemotherapy and biochemotherapy in sinonasal melanoma is limited. Bartell et al⁴⁹ reported on 15 patients who received various biochemotherapy regimens for advanced head and neck mucosal melanoma. After a median follow-up of 13 months, 3 patients (20%) had partial response, and 4 patients (27%) had complete response. The median time to disease progression for all 15 patients was 10 months and the median overall survival duration for all patients was 22 months. They concluded that biochemotherapy for advanced head and neck mucosal melanoma should be considered as a systemic treatment option both as adjuvant therapy for metastatic disease as well as neoadjuvant therapy for patients with aggressive or extensive local disease.

The decrease in survival for triple therapy versus surgery + chemotherapy in our data may well be due to a higher stage in the triple therapy group. It is difficult to definitively answer

this due to the limited patient-specific data available in the manuscripts analyzed. The statistically significant increase in overall survival for surgery + chemo- or biochemotherapy versus surgery alone and chemotherapy alone is, to our knowledge, the first demonstrated increase in overall survival in sinonasal melanoma for combined therapy. It seems likely that this is due to response to chemo- and biochemotherapy of metastatic disease, as several studies have demonstrated the lack of improvement in overall survival with improvement in local control. Again, the limited patient-specific data provided makes this difficult to establish, but it seems clear that systemic therapy improves overall survival while the addition of radiotherapy does not significantly improve overall survival, but may improve local control.

There are several weaknesses of this study. First, the retrospective data makes selection bias a possibility. However, it is extremely difficult to assemble single- or multicenter prospective trials for uncommon tumors such as sinonasal melanoma. A randomized prospective multicenter trial for sinonasal melanoma would potentially allow better standardization of treatment regimens as well as more accurate comparison of local control, disease-free survival, and overall survival between treatment modalities. The varying lengths of follow-up is another issue, however most studies followed patients for several years, and in many cases the case series included patients over the course of a decade. Given the relatively constant average survival for sinonasal melanoma, \sim 2 years, we believe this gives fairly accurate longitudinal follow-up in the data included in our meta-analysis. Another weakness is the inclusion of chemotherapy with biochemotherapy and immunotherapy as a single group. A more specific subgroup analysis by specific treatment regimen would be ideal, however the limited number of patients with sinonasal melanoma and the lack of individual data on each patient makes this difficult. As other large series such as the Ives meta-analysis⁴⁸ grouped different regimens together and found significant differences which were maintained whether the chemo- and biochemotherapy groups were analyzed separately or as subgroups, we believe this does not significantly affect the overall improvement on survival found in this meta-analysis.

Conclusion

To our knowledge, this is the largest meta-analysis of patients with primary sinonasal melanoma. The data demonstrates that there is no survival advantage for combined radiotherapy + surgery or chemoradiotherapy + surgery versus surgery alone. We did find a significant overall survival advantage for surgery + chemotherapy versus surgery alone and versus chemotherapy alone. The average overall survival was 27.41 months for all therapies, confirming past studies pointing to a fairly dismal prognosis for this rare malignancy. We therefore recommend aggressive treatment primarily with surgery for resectable disease with the goal of achieving local control, with the caveat that a significant number of patients will have distant recurrence (44% in our dataset) which is not significantly impacted by adjuvant treatment such as

radiotherapy. It appears that improvements in overall survival must result from improvements in response of metastatic disease and distant recurrences with chemotherapy, immunotherapy, or biochemotherapy. We recommend aggressive surgical resection as the primary modality, combined with radiotherapy as necessary for local control. We recommend chemotherapy and biochemotherapy as both adjuvant treatment for distant disease as well as neoadjuvant chemotherapy as this appears to improve overall survival. In conclusion, this meta-analysis is, to our knowledge, the largest meta-analysis of patients with mucosal melanoma of the nasal cavity/paranasal sinuses. It confirms earlier retrospective studies demonstrating that sinonasal melanoma has a poor prognosis, with survival on the order of 24 months. It also demonstrates that the addition of radiotherapy to surgical resection does not significantly improve overall survival, but that overall survival is improved with combined surgery + chemotherapy.

Note

Presented at the 20th Annual North American Skull Base Society Meeting, New Orleans, LA, October 14th to 18th, 2009.

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