**Title:**

Evaluation of head and neck mucosal melanoma and proposal of a novel stage grouping system

**Principal Investigator:**

Name: A.P.

Email:

**CoC accredited program:**

Methodist Nebraska Health System, Omaha, Nebraska

**Disease site:**

Oral cavity C00.0-06.9

Oropharynx C09.0-10.9

Nasopharynx C11.0-11.9

Hypopharynx 12.9-13.9

Nasal cavity C30.0

Paranasal sinus C31.0-31.1

Larynx C32.0-32.9

**Patient age cohort of interest:** Adults 18- 90+

**Biosketch:** See attached biosketch

**Research Questions/ Objectives:**

Assess interactions of patient age, gender, race, tumor size, tumor location, extent of invasion, nodal disease, metastatic disease, treatment modality and margin status on overall survival and metastasis free survival on patient with mucosal melanoma of the head and heck.

**Background:**

Head and neck mucosal melanoma (HNMM) is a rare neoplasm, accounting for 1–4% of all melanomas, 55% of all mucosal melanomas, and only 4% of all sinonasal malignancies. [1] Disease developing within distinct subsites of the head and neck have disparate disease course and prognosis. [2] The most common primary is the nasal cavity (49.1%), followed by paranasal sinuses (23.1%), oral cavity (18.8%) and nasopharynx (5.5%). [3] Lesions within the pharynx and larynx are reported within the literature, but are rare. [4] Nodal disease also varies by primary subsite, with 13% of HNMM presenting with nodal disease, but 6.3% for nasopharynx tumors, 9.0% for oral cavity, 13.4% for nasal cavity, 14.3% for paranasal sinus, and 20.0% for oropharynx tumors. [3]

It is highly aggressive and is associated with very poor prognosis with 5-year survival rate ranging from 20-40%, median progression free survival of only 24 months and between 39% and 68% eventually developing metastasis. [1, 2, 5] Primary treatment is typically surgical with adjuvant radiation therapy. Neck dissection can be performed for clinically positive nodes, but due to the low likelihood of regional recurrence (<15%), elective neck dissection is traditionally not recommended. [2] Growing evidence has pointed to the potential role of immunotherapy for distant metastatic disease, and potentially for locally aggressive disease. [2, 6]

Unlike cutaneous melanoma, traditional histologic grading schema cannot be applied to mucosal disease, as the mucosa lacks the histologic landmarks analogous to the papillary and reticular dermis. [4] The Ballantyne staging system, first proposed in 1970, relied on a broad discrimination between local disease (Stage I), nodal involvement (Stage II) and metastatic disease (Stage III). [7] However, HNMM, specifically sinonasal MM (SNMM) have been shown to rarely involve nodal disease and the absence of nodal involvement does not confer a significantly improved overall survival that would justify it as a dedicated stage of disease. [8] Prasad et al. proposed a modification to this system discriminating “microstages” as melanoma in situ (level I), invasion limited to the lamina propria (level II) or invasion into deep tissue (level III). [4] This approach was limited by the need for post-surgical evaluation prior to staging, as well as the increased error induced with endoscopic resection and microdebriding, where the depth is not always discernable.[1, 9]

Due to the rarity of this disease, the difficulty of pathologic diagnosis, and the overlap it shares with other pathologies within the head and neck, a separate TNM system was only established for mucosal melanoma within the AJCC, eighth edition.[6] They established T3, T4a and T4b, as well as N0-1 and M0-1. However, at the time, it was noted that insufficient data was available to establish prognostic staging groups. [6] Since then, additional research has shown the prognostic value of a number of tumor characteristics, specifically tumor size and volume[5], depth of invasion [4], head and neck subsite involvement [1], nodal involvement [8], presence of positive margins and metastatic disease[2]. While several authors have identified poor prognostic factors or proposed novel risk stratifications schema, there has not been a systemic study to establish and validate a prognostic staging system. Such prognostic staging system provide important information to health care providers, researchers and patients. It allows patients with similar prognoses to be grouped for appropriate treatment and research purposes. It also allows patients and providers realistic and actionable expectations of the expected disease course. [10]

**Objectives:**

* Identify interaction of age, gender, race, tumor size, tumor location, extent of invasion, nodal disease, metastatic disease, treatment modality and margin status in head and neck mucosal melanoma and identify its impact on
  + Overall survival
  + Disease specific survival
  + Disease free survival
  + Metastasis free survival
  + Nodal/ regional failure rate
* Use the identified high-risk factors to form novel prognostic groupings

**Analysis plan:**

Study type: Retrospective evaluation of NCDB data

Patient selection: Adults (ages 18-90+)

Histology: Melanoma, mucosal (WHO Tumor Code 8720, 8722, 8770, 8771, 9772)

Stage selection:

T stage- Any T

N stage- N0 only

M stage- M0 or Mx

**Study period:** 2004- 2017

**Inclusion criterion:**

* Mucosal melanoma of the head and neck

**Data points of interest:**

* Demographic variables
* Comorbid conditions ,
* Charlson Comorbid Index (CCI) (Charlson-Deyo Score: 0,1,2,3+)
* Stage information (TNM and prognostic staging)
  + Clinical
  + Pathologic
  + Collaborative
* Disease primary site
* Histologic characteristics and subtype (epithelioid, spindle, mixed, or undifferentiated)
* Treatment variables
  + Primary site
    - Margin status
  + Nodal basin
  + Use of radiation
  + Use of chemotherapy/ immunotherapy
* Survival outcomes
  + Overall survival
  + Disease specific survival
  + Disease free survival
  + Metastasis free survival
  + Nodal/ regional failure rate

**Data analysis plan:**

Retrospective review of the dataset, which will be evaluated for data points listed above. Relationship of age adjusted comorbidity index to node status, and its impact on survival outcomes will be evaluated, using multivariate logistic regression and Cox proportional hazard analyses.

Kaplan-Meier survival curves will be plotted and compared between patient cohorts. Analyses will be performed with use of SPSS v20 and SAS as applicable. Chi-square tests and Fisher Exact test will be used where appropriate. Analyses will be controlled for age, gender, stage, Charlson-Deyo scores, geography, and other socio-economic factors. Then, using, recursive partitioning analysis (RPA), establish a stage grouping system.

**Clinical relevance:**

* Identification of high-risk factors of mucosal melanoma
* Develop and validate a novel prognostic staging system to be use in the direction of future treatment, research and patient education.

**Citations:**

1. Moya-Plana, A., et al., *Risk-based stratification in head and neck mucosal melanoma.* Oral Oncol, 2019. **97**: p. 44-49.

2. Ganti, A., et al., *Treatment modalities in sinonasal mucosal melanoma: A national cancer database analysis.* Laryngoscope, 2020. **130**(2): p. 275-282.

3. Jethanamest, D., et al., *Predictors of survival in mucosal melanoma of the head and neck.* Ann Surg Oncol, 2011. **18**(10): p. 2748-56.

4. Prasad, M.L., et al., *Primary mucosal melanoma of the head and neck: a proposal for microstaging localized, Stage I (lymph node-negative) tumors.* Cancer, 2004. **100**(8): p. 1657-64.

5. Flukes, S., et al., *Primary tumor volume as a predictor of distant metastases and survival in patients with sinonasal mucosal melanoma.* Head Neck, 2020. **42**(11): p. 3316-3325.

6. Lydiatt, W., et al., *Mucosal Melanoma of the Head and Neck*, in *AJCC Cancer Staging Manual, Eighth Edition*, A.e. al, Editor. 2017, Springer: New York. p. 163-169.

7. Ballantyne, A., *Malignant melanoma of the skin of the head and neck. An analysis of 405 cases.* Am J Surgery, 1970. **120**(4): p. 425-31.

8. Amit, M., et al., *Approaches to regional lymph node metastasis in patients with head and neck mucosal melanoma.* Cancer, 2018. **124**(3): p. 514-520.

9. Michel, J., et al., *Sinonasal mucosal melanomas: the prognostic value of tumor classifications.* Head Neck, 2014. **36**(3): p. 311-6.

10. Lee, N.C.J., et al., *Evaluation of head and neck soft tissue sarcoma 8th edition pathologic staging system and proposal of a novel stage grouping system.* Oral Oncol, 2021. **114**: p. 105137.

**What statistical software will be used:**

SPSS, SAS

**How is the study funded:**

Internal institutional support

**How long will the proposed research take to complete?**

6 months