# International multi-center study of clinical outcomes of sinonasal melanoma shows survival benefit for patients treated with immune checkpoint inhibitors and potential improvements to the current TNM staging system

*Running Title: Clinical outcomes in sinonasal mucosal melanoma*

*Matt Lechner MD, PhD[1,2,3,*], Yoko Takahashi PhD[4,*], Mario Turri-Zanoni MD[5], Marco Ferrari MD[6], Jacklyn Liu MSc[1], Nicholas Counsell MSc[7], Davide Mattavelli MD PhD[8], Vittorio Rampinelli MD[8], William Vermi MD PhD[8], Davide Lombardi MD[8], Rami Saade MD[4,9], Ki Wan Park MD[10], Volker H Schartinger MD[11], Alessandro Franchi MD[12], Carla Facco MD[13], Fausto Sessa MD[13], Simonetta Battocchio MD[14], Tim R. Fenton PhD[15], Francis M Vaz MBBS[16], Paul O'Flynn MBBS[16], David Howard FRCS[16], Paul Stimpson FRCS (ORL-HNS)[16], Simon Wang MBBS[17], S. Alam Hannan FRCS(ORL-HNS)[16], Samit Unadkat FRCS(ORL-HNS)[16], Jonathan Hughes PhD FRCS[18], Raghav Dwivedi PhD FRCS (ORL-HNS)[18], Cillian T. Forde MRCS[16], Premjit Randhawa MSc(Hons) FRCS (ORL-HNS)[16], Simon Gane FRCS (ORL-HNS) MPhil MBChB DOHNS[16], Jonathan Joseph MBBS FRCS (ORL-HNS)[16], Peter J. Andrews, BSc(Hons) MD FRCS (ORL-HNS)[16], Manas Dave MFDS RCPS(Glasg) FHEA[19], David Thomson MD MRCP FRCR [20,21], Tianyu Zhu PhD[22], Andrew Teschendorff PhD[22], Gary Royle PhD[1], Christopher Steele PhD[1], Joaquin E. Jimenez MD[23], Jan Laco, PhD[24], Eric W. Wang MD[23,25], Carl Snyderman MD MBA[23,25], Peter D. Lacy FRCSI[26], Robbie Woods MD FRCSI[26], James P. O'Neill MD, FRCSI[26,27], Anirudh Saraswathula MD[28], Raman Preet Kaur PhD[28], Tianna Zhao PhD[29], Murugappan Ramanathan Jr. MD[28,29], Gary L. Gallia MD PhD[28,29,30], Nyall London MD PhD[28,29,31], Quynh-Thu Le MD[32], Robert B. West MD[32], Zara M. Patel MD[10], Jayakar Nayak MD PhD[10], Peter H. Hwang MD FACS[10], Mario Hermsen PhD[33], Jose Llorente MD PhD[33], Fabio Facchetti MD PhD[14], Piero Nicolai MD[6], Paolo Bossi MD[34], Paolo Castelnuovo MD PhD[5], Amrita Jay MFDSRCS[35], Dawn Carnell MBBS[18], Martin D Forster MBBS PhD[1], Diana M. Bell MD[36], Valerie J. Lund MS FRCS, FRCSEd[16] and Ehab Y Hanna MD FACS[4]*

*Affiliations*

1.     UCL Cancer Institute, University College London, London, UK

2.     UCL Division of Surgery and Interventional Science, University College London, London, UK

3.     ENT Department, Barts Health NHS Trust, London, UK

4.       Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, USA

5.       Unit of Otorhinolaryngology - Head & Neck Surgery, Department of Biotechnology and Life Sciences, University of Insubria, Varese, Italy

6.       Section of Otorhinolaryngology – Head and Neck Surgery, Department of Neurosciences, University of Padova, Italy

7.       Cancer Research UK & UCL Cancer Trials Centre, University College London, London, UK

8.       Unit of Otorhinolaryngology – Head and Neck Surgery, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy

9.       Department of Otolaryngology Head and Neck Surgery, Lebanese American University, Beirut, Lebanon

10.     Rhinology & Endoscopic Skull Base Surgery, Department of Otolaryngology-H&N Surgery, Stanford University School of Medicine, Palo Alto, USA

11.     Department of Otorhinolaryngology, Medical University of Innsbruck, Innsbruck, Austria

12.     Department of Translational Research, University of Pisa, Pisa, Italy

13.     Unit of Pathology, ASST Sette Laghi, University of Insubria, Varese, Italy

14.     Pathology Unit, Department of Molecular and Translational Medicine, University of Brescia, ASST Spedali Civili, Brescia, Italy

15.     Cancer Sciences Unit, Faculty of Medicine, University of Southampton, UK

16.     Royal National ENT Hospital and Head and Neck Centre, University College London Hospitals NHS Trust, London, UK

17.     Department of Oncology, Haematology and Bone Marrow Transplantation with Section Pneumology, Hubertus Wald Tumorzentrum, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

18.     Head and Neck Centre, University College London Hospitals NHS Trust, London, UK

19.     Division of Dentistry, University of Manchester, Manchester, UK

20.     Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester, UK

21.     Division of Cancer Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, The Christie NHS Foundation Trust, Manchester, UK

22.     CAS Key Laboratory of Computational Biology, Shanghai Institute of Nutrition and Health, University of Chinese Academy of Sciences, Shanghai, China

23.     Department of Otolaryngology, University of Pittsburgh Medical Center, Pittsburgh, USA

24.     The Fingerland Department of Pathology, Charles University Faculty of Medicine and University Hospital Hradec Kralove, Czech Republic

25.     Center for Cranial Base Surgery, University of Pittsburgh Medical Center, Pittsburgh, USA

26.     Department of Otolaryngology, Head and Neck Surgery, Beaumont Hospital, Dublin, Ireland

27.     The Royal College of Surgeons in Ireland, Dublin, Ireland

28.     Department of Otolaryngology—Head and Neck Surgery, Johns Hopkins School of Medicine, Baltimore, USA,

29.     Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, USA

30. Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, USA

31. Sinonasal and Skull Base Tumor Program, Head and Neck Surgery Branch, National Institute on Deafness and Other Communication Disorders, National

   Institutes of Health, Bethesda, MD, USA

32. Department of Radiation Oncology, Stanford University School of Medicine, Palo Alto, USA

33. Department of Head and Neck Oncology, Instituto de Investigación Sanitaria del Principado de Asturias, Oviedo, Spain.

34. Medical Oncology, Department of Medical and Surgical Specialities, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy

35. Department of Histopathology, University College London Hospitals NHS Trust, London, UK

36. Disease Team Alignment: Head and Neck, City of Hope Medical Center, Duarte, US


Corresponding Authors:

Matt Lechner, MD PhD

UCL Cancer Institute, University College London, London, UK; +44 7535 660441; m.lechner@ucl.ac.uk


Valerie J. Lund, MS FRCS FRCSEd

Royal National ENT Hospital and Head and Neck Centre, University College London Hospitals NHS

Trust, London, UK; v.lund@ucl.ac.uk


Ehab Y. Hanna, MD FACS

Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston,

USA; eyhanna@mdanderson.org

MD Anderson Cancer Center, Houston, TX, US; eyhanna@mdanderson.org

**Abstract**

*Objectives:* Sinonasal mucosal melanoma (SNMM) is an extremely rare and challenging sinonasal malignancy with poor prognosis. Standard treatment involves complete surgical resection, but the role of adjuvant therapy remains unclear. Crucially, our understanding of its clinical presentation, course and optimal treatment remains limited and few advancements in improving its management have been made in the recent past *Methods:* We conducted an international multi-center retrospective analysis of 505 SNMM cases from eleven institutions across the United States, United Kingdom, Ireland, and continental Europe. Data on clinical presentation, diagnosis, treatment, and clinical outcomes were assessed. *Results:* One-, 3- and 5-year recurrence-free and overall survival were 61.4%, 30.6% and 22.0%, and 77.6%, 49.2% and 38.3, respectively. Compared with disease confined to the nasal cavity, sinus involvement confers significantly worse survival; based on this, further stratifying T3 stage was highly prognostic ($p<0.001$) with implications for a potential modification to the current TNM staging system. There was a statistically significant survival benefit for patients who received adjuvant radiotherapy, compared with those who underwent surgery alone (HR=0.74, 95% CI: 0.57-0.96, *p*=0.021). Immune checkpoint blockade for the management of recurrent or persistent disease, with or without distant metastasis, conferred longer survival (HR=0.50, 95% CI: 0.25-1.00, p=0.036). *Conclusions:* We present findings from the largest cohort of SNMM reported to date. We demonstrate the potential utility of further stratifying T3-stage by sinus involvement and present promising data on the benefit of immune checkpoint inhibitors for recurrent, persistent, or metastatic disease with implications for future clinical trials in this field.

**Introduction**

Sinonasal mucosal melanoma (SNMM) is a rare, aggressive and challenging malignancy comprising 4% of all sinonasal malignancies. Tumors are often detected at a late stage resulting in poor patient prognosis, with 5-year overall survival below 25%.[1-3] Standard-of-care comprises surgical resection, with comparable outcomes between open or endoscopic approaches in well selected patients.[4,5] The efficacy of adjuvant radiotherapy and the use of systemic therapy are controversial.[6-8] Most patients will experience persistent disease or recurrence, for which treatment options are limited. Distant metastasis is the most common cause of treatment failure, having been reported in 35% of patients.[2]

To improve SNMM patient survival outcomes, use of biochemotherapy and immunotherapy has been the subject of research for the past two decades. Based on the efficacy of biochemotherapy along with interferons and/or interleukins in cutaneous melanoma, it has been widely used as part of adjuvant therapy for the management of SNMM. However, its safety and efficacy are unclear and remains to be elucidated in this disease type. Importantly, due to a lack of large-scale studies, the use of biochemotherapy for SNMM has significantly decreased in recent years. FDA-approved immune checkpoint inhibitors ipilimumab, pembrolizumab and nivolumab have been used for the treatment of SNMM, particularly in the metastatic setting, but no formal trials have been completed to date. Preliminary evidence from a small case study of SNMM has demonstrated the potential efficacy of these drugs, with durable response and acceptable

toxicities in two distant metastatic cases.[9] In their analysis of the National Cancer Database, Ganti *et al.,* suggested improved survival in patients exhibiting metastatic disease when treated with immunotherapy.[10]

Due to the rarity of this malignancy, evidence has been limited to small cohort studies or case series and analyses of existing databases. Here, we present the largest cohort of SNMM reported to date, consisting of data from eleven centers across the USA, continental Europe, UK and Ireland. We investigated potential prognostic factors, compared treatment approaches, and provide an up-to-date evaluation of immunotherapy for the management of recurrent or persistent disease.

**Materials and Methods**

*Patients*

De-identified data on 505 SNMM patients diagnosed between 1999 to 2021 was obtained from four institutions in the USA (The University of Texas MD Anderson Cancer Center, Stanford University School of Medicine, Johns Hopkins University School of Medicine and the University of Pittsburgh School of Medicine), four institutions in continental Europe (University of Insubria, Italy; ASST Spedali Civili-Università degli Studi di Brescia, Italy; Instituto de Investigacion Sanitaria del Principado de Asturias, Spain and University Hospital Hradec Kralove, Czech Republic), two institutions in the United Kingdom (University College London/University College London Hospitals, University of Manchester) and one in Ireland (Beaumont Hospital). Inclusion criteria required confirmed histopathological diagnosis of SNMM with histological characterization confirmed by head and neck pathologists experienced in the evaluation of SNMM. Data collected included

patient demographics, disease status at presentation, treatment details and patient outcomes. IRB approval was obtained from all institutions with further approval for multi-center data analysis from University College London IRB/Research Ethics Committee (UCL REC no. 9609/002; ML/VJL).

*Diagnosis and Treatment of SNMM*

The date of diagnosis was defined as the date of tissue extraction for histological determination of the diagnosis. Patients were treated as per their respective institution's standard-of-care and all institutions involved are tertiary level centers with longstanding experience in the diagnosis and management of this disease.

*Statistical Analysis of Clinical Data*

The primary aim of this study was to investigate prognostic factors of SNMM patients in terms of disease-free (DFS) and overall survival (OS), calculated from the date of diagnosis and censored at the date the patient was last known to be alive if no event had occurred. DFS and OS are described using the Kaplan-Meier method and log-rank tests. Univariable and multivariable Cox regression analyses were used to derive hazard ratios, 95% confidence intervals and corresponding p-values, both unadjusted and after accounting for other factors. Associations with the following factors were explored: age, sex, smoking status, alcohol consumption, tumor stage (staging of all the included cases was classified as T3 or greater, reflecting the most recent edition of the AJCC staging system), extent of disease at presentation and treatment approach. Statistical

significance was defined as 2-sided *p*-value < 0.05. The data analysis was generated using IBM SPSS Statistics for Windows version 27.0 (IBM Corp., Armonk, NY, USA).

**Results**

*Patient Characteristics*

The median age of patients at the time of disease diagnosis was 67.0 years (range = 15 - 93) and 53.7% were females. 48.5% and 44.2% of patients had a history of tobacco use and alcohol consumption, respectively (Table 1).

Most patients presented with T3 disease (239/398, 60.1%), followed by T4a (120/398, 30.2%) and T4b (39/398, 9.8%). At presentation, nodal disease (43/490, 8.8%) and metastatic disease (20/349, 5.7%) were uncommon. The sinuses and nasal cavity were involved in 40.4% (199/492) and 87.1% (411/472) of tumors, respectively. Skull base involvement was observed in 25.1% (65/259) of patients, however, intracranial involvement was rare (15/275, 5.5%) (Table 1).

The most common surgical findings were bony invasion (51/153; 33.3%), orbital invasion (33/210, 15.7%), cartilage invasion (20/143; 14.0%) and perineural invasion (13/115; 11.3%).

*Patient Outcomes and Prognostic Factors*

After a median follow-up of 21.3 months (N=467), 1-, 3- and 5-year OS rates were 77.6% (95% CI: 73.4%-81.2%), 49.2% (95% CI: 44.2%-54.0%) and 38.3% (95% CI: 33.2%-43.4%), respectively (Figure 1). Disease-free survival (DFS) data was available for 309 patients (Figure 2), with 1-, 3- and 5-year DFS rates of 61.4% (95% CI: 55.4%-

66.8%), 30.6% (95% CI: 25.2%-36.1%) and 22.0% (95% CI: 17.0%-27.5%). For recurrent or persistent disease, these occurred locally, regionally and locoregionally in 29.7% (76/256), 5.9% (15/256) and 8.6% (22/256) of patients, respectively. Distant metastasis was observed in 55.9% (143/256) of patients.

Upon univariable survival analysis, there was evidence that higher T-stage ($HR_{T4a \text{ vs. } T3}$=1.32, 95% CI: 0.99-1.75; $HR_{T4b \text{ vs. } T3}$=1.97, 95% CI: 1.27-3.06, p=0.007), M1-stage disease (HR=1.88, 95% CI: 1.11-3.19, p=0.031), sinus involvement (HR=1.54, 95% CI: 1.21-1.95, p<0.001), skull base involvement (HR=1.79, 95% CI: 1.24-2.58, p=0.003), and intracranial involvement (HR=3.82, 95% CI: 2.05-7.14, p<0.001) were associated with worse OS, whilst a trend towards improved survival was observed for female gender (HR = 0.79, 95% CI: 0.63-1.00, p=0.052) and nasal involvement (HR=0.70, 95% CI: 0.49-1.00, p=0.058). Sinus involvement and intracranial involvement were each independent prognostic factors in multivariable analysis (Table 2).

For DFS, nasal involvement was associated with improved survival (HR=0.57, 95% CI: 0.38-0.86, p=0.011) while intracranial involvement was associated with worse survival (HR=4.48, 95% CI: 1.94-10.3, p=0.004) (Table 2) upon univariable analysis. No other variables were significantly prognostic of DFS.

On univariable analysis, T-staging was significantly prognostic (Figure 3) whilst sinus involvement of the original disease conferred significantly worse outcome (Figure 4) and, compared to an absence of sinus involvement, was associated with positive surgical margins (37.7% vs. 21.1%, p=0.008), skull base involvement (34.3% vs. 18.1%%, *p*=0.004), bony invasion (50.0% vs. 20.2%, p<0.001), cartilage invasion (25.8% vs. 3.8%, p<0.001), and orbital invasion (25.4% vs. 4.3%, p<0.001) (Supplementary Table

1). When looking at T-staging, while T4b conferred substantially worse survival, the delineation of the survival curves between T3 and T4a was less clear, prompting us to determine the utility of integrating sinus involvement as part of T-staging. The model of T3 and T4 disease, where T3 was stratified by tumor site being nasal only or involving the sinuses, had strong prognostic value (p<0.001, Figure 5) and demonstrated that there exists a subgroup of patients within T3 disease who have worse survival, at least in part due to sinus involvement and that this group has similar outcome to T4a disease. To build on this, a model of T-staging, where T3 with sinus involvement and T4a were combined, was evaluated and found to be significantly prognostic (p<0.001, Figure 6).

*Treatment Approaches and Role of Immunotherapy*

Surgery was performed in 89.3% (431/483) of patients, among these 40.7% (197/483) underwent surgery alone whilst 44.5% (215/483) received adjuvant radiotherapy as well. Very few patients received adjuvant chemotherapy (54/483, 11.2%) (Table 3a). There was evidence that patients who received adjuvant radiotherapy had moderately better OS compared to those who underwent surgery alone (HR=0.74, 95% CI: 0.57-0.96, p=0.021, Figure 7a), and may have longer local recurrence-free survival (HR=0.62, 95% CI: 0.37-1.04, p=0.066, Figure 7b), however the evidence for the latter is less robust. Overall survival was also improved for those who underwent endoscopic resection compared to combined/open surgery (HR=0.76, 95% CI: 0.58-0.99, p=0.039, Table 3b and 4), although a selection bias for more limited disease for endoscopic resection is likely. The addition of adjuvant chemotherapy to adjuvant radiotherapy appears to have been detrimental (HR=1.65, 95% CI: 0.92-2.97, p=0.114), although the

number of patients receiving surgery and adjuvant chemoradiotherapy are small. Moreover, this observation is likely confounded by the severity of disease which may have informed the treatment approach at the outset (Table 4).

For the management of recurrent or persistent disease, with or without distant metastasis (n=99), 57.0%, 37.4% and 41.4% of patients underwent surgery, radiotherapy, and chemotherapy, respectively, either unimodally or in combination. Interferon and/or interleukin (i.e. biochemotherapy) and immune checkpoint inhibitors (ipilimumab, pembrolizumab or nivolumab) were administered to 15.2% and 27.3%, respectively, either on its own or as part of multimodal care (Table 5). In exploratory analyses, the addition of immune checkpoint inhibitors at any point in the management of recurrence/persistent disease conferred a significant overall survival benefit (HR=0.50, 95% CI: 0.25-1.00, p=0.036) (Figure 8). This effect was also seen when considering patients with distant metastatic disease as a single group (HR=0.25, 95% CI: 0.09-0.74, p=0.004) (Figure 9). Conversely, biochemotherapy does not appear to improve survival (HR=1.76, 95% CI; 0.90-3.43, p=0.119).

**Discussion**

This study's findings are based on the largest cohort of SNMM reported to date, comprising an international collaborative effort across eleven tertiary referral centers. Our analysis demonstrates extremely poor outcomes for SNMM, in line with previous literature with half of patients recurring within the first year and 5-year survival of less than 40%.

As previously reported, involvement of the paranasal sinuses confers significantly worse outcomes.[2,11-14] In the present study, sinus involvement was more common in the

maxillary and ethmoids and less frequently observed in the sphenoid or frontal sinuses. Nevertheless, involvement of any of these was associated with worse outcome. Furthermore, sinus involvement was significantly associated with more invasive disease, confirming previous findings where tumors in the paranasal sinuses had higher rates of local invasion.[2] Some authors postulate that this may be due to delayed diagnosis of disease involving the sinuses and tumors less amenable to surgery due to anatomical constraints. Lastly, whilst T-staging appears to adequately delineate prognostic groups, in our exploratory analysis, sinus involvement was able to identify a subgroup of T3 cases, which had worse outcome compared to those with nasal involvement only. Analyzing a series of 18 patients, Houette *et al.* suggest that in addition to standard staging practice, clinical management should consider tumor site as a significant prognosticator and allocate treatment accordingly.[14] In our cohort we demonstrate that outcomes of patients with T3 disease with sinus involvement appear to be similar to those with T4a disease. Based on these findings, we propose an adaptation of the currently used TNM staging system for sinonasal melanoma, i.e. the INSICA (International Network of Sinonasal Cancers; www.insica.org) modification. If adapted in an updated version of the TNM staging system, this would combine the group of patients with T3 disease with sinus involvement and patients with T4a disease and, in essence, expand the current definition of T4a disease to 'T4a: moderately advanced local disease in which tumor involves paranasal sinuses, deep soft tissue, cartilage, bone, or overlying skin' with T3 disease encompassing patients with disease in the nasal cavity only.

Management of SNMM remains challenging with most patients experiencing recurrent, persistent, or distantly metastatic disease. For the treatment of primary

disease, current surgical approaches, i.e. open or endoscopic, are comparable in appropriately selected patients. Regarding adjuvant radiotherapy, its use has been controversial, as previously-published data suggests that it may only improve local control of disease without impacting overall survival rates.[15] In the present study, we observed improved OS for those who underwent adjuvant radiotherapy, compared to surgery alone. Furthermore, there was a signal that adjuvant radiotherapy may prolong local recurrence-free survival, however, further studies are warranted to confirm these findings. Moreover, with the prospect of further developments in the field of irradiation, these technological advancements have the potential to be used for this disease, e.g. proton or carbon ion radiation therapy, which has been used in both non-surgical protocols concurrent to chemotherapy as well as in the adjuvant setting in head and neck mucosal melanoma.[16] Regarding surgical approach, we did not observe a substantial difference in survival between those who underwent endoscopic resection compared to open/combined approaches, highlighting that endoscopic surgery for well-selected cases is an effective approach, especially when taking into account the potential benefits to the patient's quality of life and morbidity.[4,17,18] Lastly, recent molecular studies showed that a proportion of tumors harbor NRAS, KIT or BRAF mutations, which are targets for therapies successfully used for other tumours.[19,20] Prospective studies are needed to investigate the efficacy of such agents for the treatment of SNMM.

Half of our cohort experienced distant metastasis, with 44.1% experiencing local/locoregional recurrence. Surgery with or without (chemo)radiotherapy remains the mainstay of treatment for recurrent disease. However, outcomes remain poor. Encouragingly, we observed highly promising survival outcomes with the inclusion of

immunotherapy. This was particularly evident with immune checkpoint inhibitors in the multi-modal treatment plan for recurrent or persistent local, regional, and distant metastatic disease. We also observed a trend toward increased use of neoadjuvant immunotherapy but the numbers in our series limited our analysis and we were unable to draw any meaningful conclusions regarding its efficacy. Further studies are needed to confirm any potential benefit of this approach.

Improved survival of patients with metastatic cutaneous melanoma upon treatment with the anti-CTLA-4 monoclonal antibody, ipilimumab, has been previously demonstrated in a phase 3 randomized controlled trial comparing its use with or without additional glycoprotein 100 peptide vaccine.[21] The safety and efficacy of the anti-PD-1 immune checkpoint inhibitor, nivolumab, has also been demonstrated in mucosal melanoma, with superior outcomes for those who receive combination therapy of ipilimumab and nivolumab.[22] For advanced melanoma and ipilimumab-refractory melanoma, pembrolizumab (anti-PD-1) has also be shown to confer antitumor activity.[23,24] In a randomized, controlled, phase 3 study comparing pembrolizumab to ipilimumab in patients with advanced cutaneous melanoma, prolonged progression-free and OS was observed in those who received pembrolizumab.[25] Building on these, double immune checkpoint blockade, comprising a combination of anti-PD-1 and anti-CTLA-4 therapies, has been proposed in recent studies, particularly for the treatment of unresectable melanoma or for patients resistant to a single immunotherapy protocol.[26,27] Based on this and the superior survival observed in those who underwent immune checkpoint blockade for the management of recurrence, persistence or distant metastasis from cutaneous melanoma, it becomes clear that further prospective studies are warranted. These future

studies will confirm safety and efficacy of these approaches for the management of sinonasal mucosal melanoma, both in the primary and recurrent settings. Intriguingly, there is evidence to suggest that immune checkpoint inhibitors may have a radio-sensitizing effect, and therefore, a combination adjuvant immunotherapy with radiotherapy may prove to be advantageous and is the subject of an ongoing clinical trial (NCT04017897).[28]

Lastly, we observed a substantial improvement with immune checkpoint inhibitors over biochemotherapy alone, which itself does not appear to greatly impact survival. Indeed, while biochemotherapy has been widely used in the past, it has been removed from standard practice at a number of institutions due to a lack of evidence for its efficacy, as well as a high risk of associated toxicities, in line with the findings in this study.

We acknowledge that our study is limited by its retrospective design; hence, statistical analyses are limited to those of an exploratory nature and results should be considered in this context. Furthermore, inherent to this being a large-scale multi-center cohort study, heterogeneity in the data collected as well as missing data were unavoidable, even though incredible effort was made to mitigate these.

In summary, this is the largest dataset reported to date on SNMM and offers a much-needed update to our current understanding of this extremely challenging malignancy. We confirm previous findings that tumor site is significantly prognostic with worse outcomes observed for those with sinus involvement of any kind. We propose a refined staging system which takes this into account. Whilst we could not draw any confirmatory conclusions regarding the role of immunotherapy in the adjuvant setting for primary disease, the beneficial use of immune checkpoint inhibitors for recurrent,

persistent, or distantly metastatic disease may be substantial. This is of particular importance as most patients will suffer recurrence or distant metastasis, for which treatment options have traditionally been very limited. In line with our findings, further trials on immune checkpoint inhibitors are warranted in both the neoadjuvant and adjuvant treatment setting for SNMM.

*Authors' contributions*

Conception and Design: M. Lechner, Y. Takahashi, M. Turri-Zanoni, M.Ferrari, J. Liu, N. Counsell, P.H. Hwang, M. Hermsen, P. Bossi, P. Castelnuovo, D.M. Bell, V.J. Lund, E.Y. Hanna.

Development of Methodology: M. Lechner, Y. Takahashi, M. Turri-Zanoni, M.Ferrari, J. Liu, N. Counsell, P.H. Hwang, M. Hermsen, P. Bossi, P. Castelnuovo, D.M. Bell, V.J. Lund, E.Y. Hanna.

Acquisition of data: M. Lechner, Y. Takahashi, M. Turri-Zanoni, M. Ferrari, J. Liu, D. Mattavelli, V. Rampinelli, W. Vermi, D. Lombardi, R. Saade, K.W. Park, V.H. Schartinger, A. Franchi, C. Facco, F. Sessa, S. Battocchio, T. Fenton, F.M. Vaz, P. O'Flynn, P. Stimpson, S. Wang, S.A. Hannan, S. Unadkat, J. Hughes, R. Dwivedi, C.T. Forde, P. Randhawa, S. Gane, J. Joseph, P.J. Andrews, M. Dave, D. Thomson, A. Teschendorff, T. Zhu, G. Royle, C. Steele, J.E. Jimenez, J. Laco, E.W. Wang, C. Snyderman, P.D. Lacy, R. Woods, J.P. O'Neill, A. Saraswathula, R.P. Kaur, T. Zhao, M. Ramanathan Jr., G. Gallia, N. London, Q.T. Le, R.B. West, Z.M. Patel, J. Nayak, P.H. Hwang, M. Hermsen,

J. Llorente, F. Facchetti, P. Nicolai, P. Bossi, P. Castelnuovo, A. Jay, D. Carnell, M.D. Forster, D.M. Bell, V.J. Lund, E.Y. Hanna

Analysis and interpretation of data: M. Lechner, Y. Takahashi, M. Turri-Zanoni, M.Ferrari, J. Liu, N. Counsell, P.H. Hwang, M. Hermsen, P. Bossi, P. Castelnuovo, D.M. Bell, V.J. Lund, E.Y. Hanna.

Writing, review, and/or revision of the manuscript: M. Lechner, Y. Takahashi, M. Turri-Zanoni, M.Ferrari, J. Liu, N. Counsell, D. Mattavelli, D. Thomson, A.E. Teschendorff, J.E. Jimenez, J. Laco, C. Snyderman, R. Woods, P.H. Hwang, A. Saraswathula, M. Hermsen, P. Bossi, P. Castelnuovo, D.M. Bell, V.J. Lund, E.Y. Hanna.

Study supervision: M. Lechner, V.J. Lund and E.Y. Hanna

**References**

1.      Lund VJ, Chisholm EJ, Howard DJ, Wei WI. Sinonasal malignant melanoma: an analysis of 115 cases assessing outcomes of surgery, postoperative radiotherapy and endoscopic resection. *Rhinology*. Jun 2012;50(2):203-10. doi:10.4193/Rhino11.267

2.      Amit M, Tam S, Abdelmeguid AS, et al. Patterns of Treatment Failure in Patients with Sinonasal Mucosal Melanoma. *Ann Surg Oncol*. Jun 2018;25(6):1723-1729. doi:10.1245/s10434-018-6465-y

3.      Lund VJ. Sinonasal Malignant Melanoma. *Adv Otorhinolaryngol*. 2020;84:185-196. doi:10.1159/000457937

4.      Miglani A, Patel SH, Kosiorek HE, Hinni ML, Hayden RE, Lal D. Endoscopic resection of sinonasal mucosal melanoma has comparable outcomes to open approaches. *Am J Rhinol Allergy*. May 1 2017;31(3):200-204. doi:10.2500/ajra.2017.31.4435

5.      Hur K, Zhang P, Yu A, Kim-Orden N, Kysh L, Wrobel B. Open Versus Endoscopic Approach for Sinonasal Melanoma: A Systematic Review and Meta-analysis. *Am J Rhinol Allergy*. Mar 2019;33(2):162-169. doi:10.1177/1945892418822637

6.      Meleti M, Leemans CR, de Bree R, Vescovi P, Sesenna E, van der Waal I. Head and neck mucosal melanoma: experience with 42 patients, with emphasis on the role of postoperative radiotherapy. *Head Neck*. Dec 2008;30(12):1543-51. doi:10.1002/hed.20901

7.      Ajmani GS, Liederbach E, Kyrillos A, Wang CH, Pinto JM, Bhayani MK. Adjuvant radiation and survival following surgical resection of sinonasal melanoma. *Am J Otolaryngol*. Nov - Dec 2017;38(6):663-667. doi:10.1016/j.amjoto.2017.08.010

8.      Gore MR, Zanation AM. Survival in Sinonasal Melanoma: A Meta-analysis. *J Neurol Surg B Skull Base*. Jun 2012;73(3):157-62. doi:10.1055/s-0032-1301400

9.      Manton T, Tillman B, McHugh J, Bellile E, McLean S, McKean E. Sinonasal Melanoma: A Single Institutional Analysis and Future Directions. *J Neurol Surg B Skull Base*. Oct 2019;80(5):484-492. doi:10.1055/s-0038-1676355

10.     Ganti A, Raman A, Shay A, et al. Treatment modalities in sinonasal mucosal melanoma: A national cancer database analysis. *Laryngoscope*. Feb 2020;130(2):275-282. doi:10.1002/lary.27995

11.     Dauer EH, Lewis JE, Rohlinger AL, Weaver AL, Olsen KD. Sinonasal melanoma: a clinicopathologic review of 61 cases. *Otolaryngol Head Neck Surg*. Mar 2008;138(3):347-52. doi:10.1016/j.otohns.2007.12.013

12.     Khan MN, Kanumuri VV, Raikundalia MD, et al. Sinonasal melanoma: survival and prognostic implications based on site of involvement. *Int Forum Allergy Rhinol*. Feb 2014;4(2):151-5. doi:10.1002/alr.21243

13.     Roth TN, Gengler C, Huber GF, Holzmann D. Outcome of sinonasal melanoma: clinical experience and review of the literature. *Head Neck*. Oct 2010;32(10):1385-92. doi:10.1002/hed.21340

14.     Houette A, Gilain L, Mulliez A, Mom T, Saroul N. Prognostic value of two tumour staging classifications in patients with sinonasal mucosal melanoma. *Eur Ann Otorhinolaryngol Head Neck Dis*. Nov 2016;133(5):313-317. doi:10.1016/j.anorl.2016.05.008

15.     Umeda Y, Yoshikawa S, Kiniwa Y, et al. Real-world efficacy of anti-PD-1 antibody or combined anti-PD-1 plus anti-CTLA-4 antibodies, with or without radiotherapy, in advanced mucosal melanoma patients: A retrospective, multicenter study. *Eur J Cancer*. Nov 2021;157:361-372. doi:10.1016/j.ejca.2021.08.034

16.     Takayasu Y, Kubo N, Shino M, et al. Carbon-ion radiotherapy combined with chemotherapy for head and neck mucosal melanoma: Prospective observational study. *Cancer Med*. Dec 2019;8(17):7227-7235. doi:10.1002/cam4.2614

17.     Swegal W, Koyfman S, Scharpf J, et al. Endoscopic and open surgical approaches to locally advanced sinonasal melanoma: comparing the therapeutic benefits. *JAMA Otolaryngol Head Neck Surg*. Sep 2014;140(9):840-5. doi:10.1001/jamaoto.2014.1321

18.     Castelnuovo P, Lepera D, Turri-Zanoni M, et al. Quality of life following endoscopic endonasal resection of anterior skull base cancers. *J Neurosurg*. Dec 2013;119(6):1401-9. doi:10.3171/2013.8.JNS13296

19.     Turri-Zanoni M, Medicina D, Lombardi D, et al. Sinonasal mucosal melanoma: Molecular profile and therapeutic implications from a series of 32 cases. *Head Neck*. Aug 2013;35(8):1066-77. doi:10.1002/hed.23079

20.     Amit M, Tam S, Abdelmeguid AS, et al. Mutation status among patients with sinonasal mucosal melanoma and its impact on survival. *Br J Cancer*. Jun 6 2017;116(12):1564-1571. doi:10.1038/bjc.2017.125

21.     Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. Aug 19 2010;363(8):711-23. doi:10.1056/NEJMoa1003466

22.     D'Angelo SP, Larkin J, Sosman JA, et al. Efficacy and Safety of Nivolumab Alone or in Combination With Ipilimumab in Patients With Mucosal Melanoma: A Pooled Analysis. *J Clin Oncol*. Jan 10 2017;35(2):226-235. doi:10.1200/JCO.2016.67.9258

23.     Ribas A, Hamid O, Daud A, et al. Association of Pembrolizumab With Tumor Response and Survival Among Patients With Advanced Melanoma. *JAMA*. Apr 19 2016;315(15):1600-9. doi:10.1001/jama.2016.4059

24.     Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol*. Aug 2015;16(8):908-18. doi:10.1016/S1470-2045(15)00083-2

25.     Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med*. Jun 25 2015;372(26):2521-32. doi:10.1056/NEJMoa1503093

26.     Li J, Kan H, Zhao L, Sun Z, Bai C. Immune checkpoint inhibitors in advanced or metastatic mucosal melanoma: a systematic review. *Ther Adv Med Oncol*. 2020;12:1758835920922028. doi:10.1177/1758835920922028

27.     Rose AAN, Armstrong SM, Hogg D, et al. Biologic subtypes of melanoma predict survival benefit of combination anti-PD1+anti-CTLA4 immune checkpoint inhibitors versus anti-PD1 monotherapy. *J Immunother Cancer*. Jan 2021;9(1)doi:10.1136/jitc-2020-001642

28.     Kim HJ, Chang JS, Roh MR, et al. Effect of Radiotherapy Combined With Pembrolizumab on Local Tumor Control in Mucosal Melanoma Patients. *Front Oncol*. 2019;9:835. doi:10.3389/fonc.2019.00835

**Figure Captions**

**Figure 1.** Kaplan-Meier curve of overall survival.

**Figure 2.** Kaplan-Meier curve of disease-free survival.

**Figure 3.** Kaplan-Meier curve of T Staging.

**Figure 4.** Kaplan-Meier curve of sinus (maxillary, frontal, ethmoid and/or sphenoid) involvement of the primary tumour.

**Figure 5.** Kaplan-Meier curve of a modified T-staging system, where T3 has been stratified by sinus involvement.

**Figure 6.** Kaplan-Meier curve of a modified T-staging system, where T3 with sinus involvement has been combined with T4a.

**Figure 7a.** Kaplan-Meier overall survival curve of surgery only vs. surgery and adjuvant radiotherapy for the treatment of disease at presentation.

**Figure 7b.** Kaplan-Meier local recurrence-free survival curve of surgery only vs. surgery and adjuvant radiotherapy for the treatment of disease at presentation.

**Figure 8.** Kaplan-Meier curve of checkpoint inhibition compared to biochemotherapy or neither for the management of recurrent/persistent disease with or without distant metastasis.

**Figure 9.** Kaplan-Meier curve of checkpoint inhibition compared to biochemotherapy or neither for the management of recurrent/persistent distantly metastatic disease.

**Tables.**

*Table 1a.* Frequency of clinical characteristics at presentation.

|  |  | n | % |
|---|---|---|---|
| Gender | Male | 233 | 46.1 |
|  | Female | 271 | 53.7 |
| Any Tobacco Use | No | 124 | 51.5 |
|  | Yes | 117 | 48.5 |
| Any Cigarette Smoking | Never | 121 | 51.1 |
|  | Former | 86 | 36.3 |
|  | Current | 30 | 12.7 |
| Any Alcohol Consumption | Never | 130 | 55.8 |
|  | Former | 22 | 9.4 |
|  | Current | 81 | 34.8 |
| Nasal Involvement of Original Tumour at Presentation | No | 61 | 12.9 |
|  | Yes | 411 | 87.1 |
| Sinus Involvement of Original Tumour at Presentation | No | 293 | 59.6 |
|  | Yes | 199 | 40.4 |
| Skull Base Involvement of Original Tumour at Presentation | No | 194 | 74.9 |
|  | Yes | 65 | 25.1 |
| Intracranial Involvement of Original Tumour at Presentation | No | 260 | 94.5 |
|  | Yes | 15 | 5.5 |
| T-Stage | T3 | 239 | 60.1 |
|  | T4a | 120 | 30.2 |
|  | T4b | 39 | 9.8 |
| N-Stage | N0 | 447 | 91.2 |
|  | N1 | 43 | 8.8 |
| M-Stage | M0 | 329 | 94.3 |
|  | M1 | 20 | 5.7 |

**Table 1b.** *Prevalence of additional surgical findings.*

|  | n | % |
|---|---|---|
| Bony Invasion (n=153) | 51 | 33.3 |
| Lymphovascular Invasion (n=108) | 8 | 7.4 |
| Cartilage Invasion (n=143) | 20 | 14.0 |
| Perineural Invasion (n=115) | 13 | 11.3 |
| Angioinvasion (n=107) | 8 | 7.5 |
| Dural Invasion (n=227) | 7 | 3.1 |
| Brain Invasion (n=174) | 3 | 1.7 |
| Orbital Invasion (n=210) | 33 | 15.7 |

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***Table 2.*** Univariable and multivariable Cox regression overall and recurrence-free survival analyses of clinical and tumour characteristics.

| | OS - Univariable | | OS – Multivariable | | DFS – Univariable | |
|---|---|---|---|---|---|---|
| | n | HR (95% CI) *p*-value | n | HR (95% CI) *p*-value | n | HR (95% CI) *p*-value |
| Age | 458 | HR=1.01 (95% CI: 1.00-1.02) *p*=0.113 | | NA | 308 | HR=1.00 (95% CI: 0.99-1.01) *p*=0.919 |
| Gender (Female vs. Male) | 459 | HR=0.79 (95% CI: 0.63-1.00) *p*=0.052* | 231 | HR=0.89 (95% CI: 0.63-1.25) *p*=0.508 | 309 | HR=0.94 (95% CI: 0.72-1.22) *p*=0.626 |
| Tobacco (Yes vs. No) | 233 | HR=1.35 (95% CI: 0.96-1.88) *p*=0.082 | | NA | 185 | HR=0.97 (95% CI: 0.69-1.36) *p*=0.851 |
| Cigarette Smoking | | *p*=0.242 | | | | *p*=0.974 |
| Former vs. Never | 229 | HR=1.34 (95% CI: 0.93-1.93) | | NA | 181 | HR=0.1.01 (95% CI: 0.69-1.48) |
| Current vs. Never | | HR=1.34 (95% CI: 0.80-2.24) | | | | HR=0.95 (95% CI: 0.56-1.62) |
| Alcohol Consumption | | *p*=0.457 | | | | *p*=0.267 |
| Former vs. Never | 225 | HR=0.77 (95% CI: 0.41-1.45) | | NA | 178 | HR=0.59 (95% CI: 0.28-1.22) |
| Current vs. Never | | HR = 0.82 (95% CI: 0.57-1.17) | | | | HR=1.03 (95% CI: 0.71-1.48) |
| T-Stage | | *p*=0.007* | | *p*=0.923 | | *P*=0.468 |
| T4a vs. T3 | 390 | HR=1.32 (95% CI: 0.99-1.75) | 231 | HR=0.95 (95% CI: 0.64-1.42) | 305 | HR=1.12 (95% CI: 0.83-1.50) |
| T4b vs. T3 | | HR=1.97 (95% CI: 1.27-3.06) | | HR=0.87 (95% CI: 0.42-1.79) | | HR=1.29 (95% CI: 0.84-1.98) |
| N-Stage (N1 vs. N0) | 452 | HR=1.33 (95% CI: 0.86-2.05) *p*=0.224 | | NA | 306 | HR=1.51 (95% CI: 0.92-2.49) *p*=0.122 |
| M-Stage (M1 vs. M0) | 342 | HR=1.88 (95% CI: 1.11-3.19) *p*=0.031* | 231 | HR=1.87 (95% CI: 0.97-3.63) *p*=0.086 | 292 | HR=1.16 (95% CI: 0.59-2.26) *p*=0.674 |

| | | | | | |
|---|---|---|---|---|---|
| Nasal Involvement (Yes vs. No) | 427 | HR=0.70 (95% CI: 0.49-1.00) p=0.058 | | NA | 287 | HR=0.57 (95% CI: 0.38-0.86) p=0.011* |
| Sinus Involvement (Yes vs. No) | 448 | HR=1.54 (95% CI: 1.21-1.95) p<0.001* | 231 | HR=1.54 (95% CI: 1.07-2.21) p=0.022* | 300 | HR=1.15 (95% CI: 0.88-1.50) p=0.302 |
| Skull Base Involvement (Yes vs. No) | 253 | HR=1.79 (95% CI: 1.24-2.58) p=0.003* | 231 | HR=1.41 (95% CI: 0.89-2.22) p=0.153 | 209 | HR=1.02 (95% CI: 0.69-1.51) p=0.908 |
| Intracranial Involvement (Yes vs. No) | 268 | HR=3.82 (95% CI: 2.05-7.14) p<0.001* | 231 | HR=3.06 (95% CI: 1.44-6.50) p=0.007* | 219 | HR=4.48 (95% CI: 1.94-10.3) p=0.004* |
| Bony Invasion (Yes vs. No) | 150 | HR=1.38 (95% CI: 0.89-2.15) p=0.160 | | NA | 128 | HR=1.17 (95% CI: 0;77-1.76) p=0.469 |
| Lymphovascular Invasion (Yes vs. No) | 106 | HR=1.37 (95% CI: 0.55-3.46) p=0.519 | | NA | 90 | HR=1.57 (95% CI: 0.67-3.63) p=0.326 |
| Cartilage Invasion (Yes vs. No) | 140 | HR=1.42 (95% CI: 0.78-2.58) p=0.265 | | NA | 122 | HR=1.39 (95% CI: 0.80-2.41) p=0.261 |
| Perineural Invasion (Yes vs. No) | 113 | HR=1.17 (95% CI: 0.50-2.70) p=0.728 | | NA | 93 | HR=0.91 (95% CI: 0.40-2.11) p=0.831 |
| Angioinvasion (Yes vs. No) | 105 | HR=0.79 (95% CI: 0.29-2.18) p=0.638 | | NA | 86 | HR=0.65 (95% CI: 0.24-1.78) p=0.369 |
| Dural Invasion (Yes vs. No) | 225 | HR=1.35 (95% CI: 0.59-3.07) p=0.493 | | NA | 172 | HR=1.28 (95% CI: 0.56-2.91) p=0.571 |
| Brain Invasion (Yes vs. No) | 172 | HR=1.52 (95% CI: 0.48-4.82) p=0.502 | | NA | 119 | HR=1.95 (95% CI: 0.48-7.95) p=0.402 |
| Orbital Invasion (Yes vs. No) | 206 | HR=1.53 (95% CI: 0.96-2.45) p=0.088 | | NA | 183 | HR=1.29 (95% CI: 0.81-2.06) p=0.294 |

**Table 3a.** Number and frequency of patients who underwent the various treatment approaches.

|  | n | % |
|---|---|---|
| None/Biopsy | 9 | 1.9 |
| Excisional Biopsy | 1 | 0.2 |
| Surgery Only | 197 | 40.8 |
| RT Only | 4 | 0.8 |
| Chemotherapy Only | 6 | 1.2 |
| Surgery and RT | 192 | 39.8 |
| Surgery and Chemotherapy | 19 | 3.9 |
| Chemoradiotherapy | 6 | 1.2 |
| Surgery and Chemoradiotherapy | 23 | 4.8 |
| Other | 4 | 0.8 |
| Immunotherapy | 17 | 3.5 |
| Biochemotherapy | 5 | 1.0 |

**Table 3b.** Number and frequency of patients who underwent endoscopic or open/combined surgery.

|  | n | % |
|---|---|---|
| Endoscopic resection | 201 | 55.1 |
| Open/Combined | 164 | 44.9 |

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***Table 4.*** Univariable Cox regression overall, disease-free and local recurrence-free survival analyses of treatment approach.

| | | **OS – Univariable** | | **DFS - Univariable** | | **LRFS** |
|---|---|---|---|---|---|---|
| | n | HR (95% CI) *p*-value | n | HR (95% CI) *p*-value | n | HR (95% CI) *p*-value |
| Endoscopic vs. Other Surgical Approach | 337 | HR=0.76 (95% CI: 0.58-0.99) *p*=0.039* | 217 | HR=0.81 (95% CI: 0.59-1.10) *p*=0.176 | 92 | HR=0.81 (95% CI: 0.44-1.49) *p*=0.495 |
| Surgery and Adj. RT vs. Surgery Alone | 363 | HR=0.74 (95% CI: 0.57-0.96) *p*=0.021* | 254 | HR=0.83 (95% CI: 0.63-1.10) *p*=0.202 | 124 | HR=0.62 (95% CI: 0.37-1.04) *p*=0.066 |
| Surgery and Adj. CRT vs. Surgery and Adj. RT | 204 | HR=1.65 (95% CI: 0.92-2.97) *p*=0.114 | 147 | HR=1.49 (95% CI: 0.79-2.78) *p*=0.239 | 65 | HR=1.15 (95% CI: 0.27-4.93) *p*=0.852 |

**Table 5.** Number and frequency of patients who underwent the various treatment approaches for the management of recurrent or persistent disease.

|  |  | Count | % |
|---|---|---|---|
| Immune Checkpoint Blockade | No | 72 | 72.7% |
|  | Yes | 27 | 27.3% |
| Interferon and/or interleukin | No | 84 | 84.8% |
|  | Yes | 15 | 15.2% |
| Chemotherapy | No | 58 | 58.6% |
|  | Yes | 41 | 41.4% |
| Surgery | No | 43 | 43.0% |
|  | Yes | 57 | 57.0% |
| Radiotherapy | No | 62 | 62.6% |
|  | Yes | 37 | 37.4% |

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***Supplemental Table 1.*** *Associations between sinus involvement and other factors.*

| | No Sinus Involvement | | Sinus Involvement | | p-value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Skull Base Involvement (n=257) | 27 | 18.1 | 37 | 34.3 | 0.004* |
| Intracranial Involvement (n=263) | 6 | 3.9 | 9 | 8.3 | 0.177 |
| Positive Surgical Margins (n=244) | 25 | 21.9 | 49 | 37.7 | 0.008* |
| Bony Invasion (n=150) | 17 | 20.2 | 33 | 50.0 | <0.001* |
| Lymphovascular Invasion (n=108) | 5 | 7.1 | 3 | 7.9 | 1.000 |
| Cartilage Invasion (n=141) | 3 | 3.8 | 16 | 25.8 | <0.001* |
| Perineural Invasion (n=114) | 5 | 6.8 | 7 | 17.1 | 0.114 |
| Angioinvasion (n=107) | 5 | 7.0 | 3 | 8.3 | 1.000 |
| Dural Invasion (n=227) | 2 | 1.8 | 5 | 4.3 | 0.446 |
| Brain Invasion (n=174) | 1 | 0.9 | 2 | 2.9 | 0.561 |
| Orbital Invasion (n=208) | 4 | 4.3 | 29 | 25.4 | <0.001* |