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

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Abstract (250 words)

Sinonasal mucosal melanoma (SNMM) is an extremely challenging sinonasal malignancy with a very poor prognosis. Treatment involves complete surgical resection while the role of adjuvant therapy remains controversial. 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. We conducted an international multi-center retrospective analysis of 480 SNMM cases from nine institutions across the United States, United Kingdom, Ireland, and continental Europe. Data on clinical presentation, diagnosis, treatment, and clinical outcomes were assessed. One-, 3- and 5-year recurrence-free and overall survival were 55.8%, 18.3% and 10.1%, and 77.6%, 49.4% and 38.7%, respectively. 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 no significant difference in overall survival between patients who received surgery alone compared to those who received adjuvant radiotherapy. Checkpoint inhibition for the management of recurrent or persistent disease, with or without distant metastasis, conferred longer survival ($p=0.009$). In conclusion, 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 checkpoint inhibitors for recurrent, persistent, or metastatic disease with implications for future clinical trials in this field.

Keywords (4-9): sinonasal mucosal melanoma, SNMM, TNM, immunotherapy, checkpoint inhibitors, sinus involvement.

Introduction

Sinonasal mucosal melanoma (SNMM) is a rare and challenging malignancy, comprising 4% of all sinonasal malignancies. Tumors are often detected at a late stage and prognosis is poor, with 5-year overall survival below 40%.[1,2] Standard-of-care comprises surgical resection, with comparable outcomes between an open or endoscopic approach.[3,4] The efficacy of adjuvant radiotherapy and the use of systemic therapy are controversial.[5-7] 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 on the poor survival outcomes associated with SNMM, the use of biochemotherapy and immunotherapy has been the subject of research for the past two decades. Based on its efficacy in cutaneous melanoma, biochemotherapy, including the use of interferon and/or interleukin, has been widely used as part of adjuvant therapy. However, their safety and efficacy remain ill-described and unclear in sinonasal melanoma due to a lack of large-scale studies and its use has significantly decreased in recent years. Since the FDA-approval of the checkpoint inhibitors ipilimumab, pembrolizumab and nivolumab, these have been used for the treatment of SNMM, particularly in the metastatic setting, but no formal trials have been completed. Preliminary evidence from a small case series of SNMM has demonstrated the potential efficacy of this approach, with durable response and acceptable toxicities in two distant metastatic

cases.[8] In their analysis of the National Cancer Database, Ganti *et al* suggested improved survival in those with metastatic disease treated with immunotherapy.[9]

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 nine centers across the USA, continental Europe, UK and Ireland. We investigate potential prognostic factors, compare treatment approaches, and provide an up-to-date evaluation of the use of immunotherapy for the management of recurrent or persistent disease.

Materials and Methods

Patients

De-identified data on 480 SNMM patients were obtained from three institutions in the USA (The University of Texas MD Anderson Cancer Center, Stanford University School of Medicine and the University of Pittsburgh School of Medicine), four institutions in continental Europe (University of Insubria, Italy; Universita degli Studi di Brescia, Italy; Instituto de Investigacion Sanitaria del Principado de Asturias, Spain and University Hospital Hradec Kralove, Czech Republic) and two institutions in the United Kingdom (University College London/University College London Hospitals) and Ireland (Beaumont Hospital). Inclusion criteria required confirmed histopathological diagnosis of SNMM with histological characterization and sample/cohort selection performed by head and neck pathologists experienced in the evaluation of SNMM. Clinical data were obtained retrospectively and reviewed by the lead team. 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 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, extent of disease at presentation and treatment approach. 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 at diagnosis was 67.0 years (range = 15 - 93) and 54.2% female, with 49.8% and 47.9% of patients having a history of tobacco use and alcohol consumption, respectively (Table 1).

Most patients presented with T3 disease (62.5%), followed by T4a (29.1%) and T4b (8.4%). At presentation, nodal disease (8.5%) and metastatic disease (5.7%) were uncommon. 42.0% of tumors involved the sinuses (24.8%, 27.3%, 9.0% and 5.8% in the maxillary, ethmoid, sphenoid, and frontal sinuses, respectively) and 86.2% involved the nasal cavity. 20.5% of patients presented with skull base involvement, however, intracranial involvement was rare (5.6%) (Table 1).

The most common surgical findings were bony invasion (51/151; 33.8%), periorbital invasion (13/76; 17.1%); cartilage invasion (19/141; 13.5%) and perineural invasion (12/111; 10.8%).

Patient Outcomes and Prognostic Factors

After a median follow-up of 21.0 months (N=436), 1-, 3- and 5-year OS rates were 77.6% (95% CI: 73.2%-81.4%), 49.4% (95% CI: 44.2%-54.4%) and 38.7% (95% CI: 33.4%-44.0%), respectively (Figure 1). Recurrence data was available for 228 patients (Figure 2), with 1-, 3- and 5-year RFS rates of 55.8% (95% CI: 49.1%-62.0%), 18.3% (95% CI: 13.5%-23.7%) and 10.1% (95% CI: 6.5%-14.7%). For recurrent or persistent disease, these occurred locally, regionally and locoregionally in 30.8%, 5.8% and 8.8% of patients, respectively. 54.6% of patients experienced distant metastasis.

There was evidence that age at diagnosis being 65 years or greater (HR=1.31, 95% CI:=1.03-1.67, p=0.026), history of tobacco use (HR=1.47, 95% CI: 1.04-2.08, p=0.030), sinus involvement (HR=1.58, 95% CI: 1.24-2.03, p<0.001), skull base involvement (HR=2.17, 95% CI: 1.52-3.09, p<0.001), higher T-stage ($HR_{T4a\ vs.\ T3}$=1.27, 95% CI: 0.93-1.72; $HR_{T4b\ vs.\ T3}$=2.70, 95% CI: 1.70-4.27, p=0.001), and M1-stage disease (HR=2.14, 95% CI: 1.24-3.70, p=0.014) were associated with worse OS whilst female gender (HR = 0.79, 95% CI: 0.62-1.00, p=0.051) was associated with superior OS in univariable analyses. In a multivariable model comprising age, gender, tobacco use, clinical T-stage, M-stage, sinus involvement, and skull base involvement, only M1-stage was significantly prognostic of overall survival (HR=2.84, 95% CI: 1.33-6.05, p=0.015) (Table 2).

For recurrence-free survival, higher T-stage ($HR_{T4a\ vs.\ T3}$=1.24, 95% CI: 0.90-1.72; $HR_{T4b\ vs.\ T3}$=2.16, 95% CI: 1.33-3.52, p=0.013), sinus involvement (HR=1.42, 95% CI: 1.06-1.89, p=0.019) and skull base involvement (HR=2.14, 95% CI: 1.43-3.20, p=0.001) were significantly prognostic upon univariable analysis. In a multivariable model of these factors, only skull base involvement remained prognostic (Table 3).

On univariable analysis, and to a lesser extent, multivariable analysis, T-staging was significantly prognostic (Figure 3) whilst sinus involvement of the original disease conferred significantly worse outcome (Figure 4) and was associated with positive surgical margins (38.2% vs. 20.8%, *p*=0.006), skull base involvement (26.1% vs. 14.4%, *p*=0.018), cartilage invasion (25.8% vs. 2.6%, *p*<0.001), and orbital invasion (25.4% vs. 4.4%, *p*<0.001)(Supplementary material). However, there was substantial overlap in the survival curves for T3 and T4a disease, 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 within T3 disease a subgroup of patients who have worse survival, at least in part due to sinus involvement and that this group have 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 was found to be significantly prognostic (p<0.001, Figure 6).

Treatment Approaches and Role of Immunotherapy

91.4% of patients underwent surgery; 42.6% underwent surgery alone whilst 40.1% also received adjuvant radiotherapy. Very few patients received adjuvant chemotherapy (8.7%) (Table 4a). There was weak evidence that patients who received adjuvant radiotherapy had moderately better OS compared to those who underwent surgery alone (HR=0.79, 95% CI: 0.61-1.03, p=0.082, Figure 7), and for those who underwent endoscopic resection compared to combined/open surgery (HR=0.83, 95% CI: 0.063-1.10, p=0.195) (Table 4b). The addition of adjuvant chemotherapy to adjuvant radiotherapy appears to have been detrimental (HR=1.96, 95% CI: 1.06-3.60, p=0.047), although patients numbers receiving surgery and adjuvant chemoradiotherapy are small, also this observation is likely confounded by the severity of disease which may have informed the treatment approach at the outset (Table 5).

For the management of recurrent or persistent disease, with or without distant metastasis, 57.0%, 37.4% and 41.4% of patients underwent surgery, radiotherapy, and chemotherapy, respectively, either unimodally or in combination. 15.2% and 27.3%

received inferno and/or interleukin (i.e. biochemotherapy) and checkpoint inhibition (ipilumumab, pembrolizumab or nivolumab), respectively, either on its own or as part of multimodal care. In exploratory analyses, the addition of checkpoint inhibition 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 reports on the largest cohort of SNMM to date, comprising an international collaborative effort across nine 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.[2,10-13] 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 were negatively prognostic. Furthermore, sinus involvement was significantly associated with more invasive disease, confirming previous findings where tumours 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 poorer outcomes 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 tumour site as a significant prognosticator and allocate treatment accordingly.[13] Following on from that, 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 tumour 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 approaches are comparable. 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.[3,14,15]

Due to the extent of disease at presentation, 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, specifically checkpoint inhibition, 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 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.[16] The safety and efficacy of the anti-PD-1 checkpoint inhibitor, nivolumab, has also been demonstrated in mucosal melanoma, with superior outcomes for those who receive combination therapy of ipilimumab and nivolumab.[17] For advanced melanoma and ipilimumab-refractory melanoma, pembrolizumab (anti-PD-1) has also be shown to confer antitumor activity.[18,19] In a randomized, controlled, phase 3 study comparing pembrolizumab to ipilimumab in patients with advanced melanoma, prolonged progression-free and overall survival was observed in those who received pembrolizumab.[20] Based on these and the superior survival observed in our cohort for those who underwent checkpoint inhibition for the management of recurrence, persistence or distant metastasis, further prospective studies are warranted to confirm the 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 checkpoint inhibition may have a radio-sensitizing effect, as such, a combination adjuvant immunotherapy with radiotherapy may prove to be advantageous and is the subject of an ongoing clinical trial (NCT04017897).[21]

Lastly, we observed a substantial improvement with checkpoint inhibition over the receipt of 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 tumour site is significantly prognostic with worse outcomes observed for those with sinus involvement of any kind. We propose a refined staging which takes this into account sinus involvement. Whilst we could not draw any confirmatory conclusions regarding the role of immunotherapy in the adjuvant setting for primary disease, the beneficial use of checkpoint inhibition 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 checkpoint

inhibitors are warranted in both the neoadjuvant and adjuvant treatment setting for SNMM.

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Conflicts of Interest (TBD)

NL receives research funding from Merck Inc., not related to this manuscript, and was a consultant for CoolTech Inc. and holds stock in Navigen Pharmaceuticals, both of which are unrelated to this manuscript. SW is on the advisory board of ALK, Genentech, OptiNose, SinopSys and a Consultant to NeurENT, Stryker, all of which are unrelated to this manuscript. All other authors declare no potential relevant conflicts of interest.

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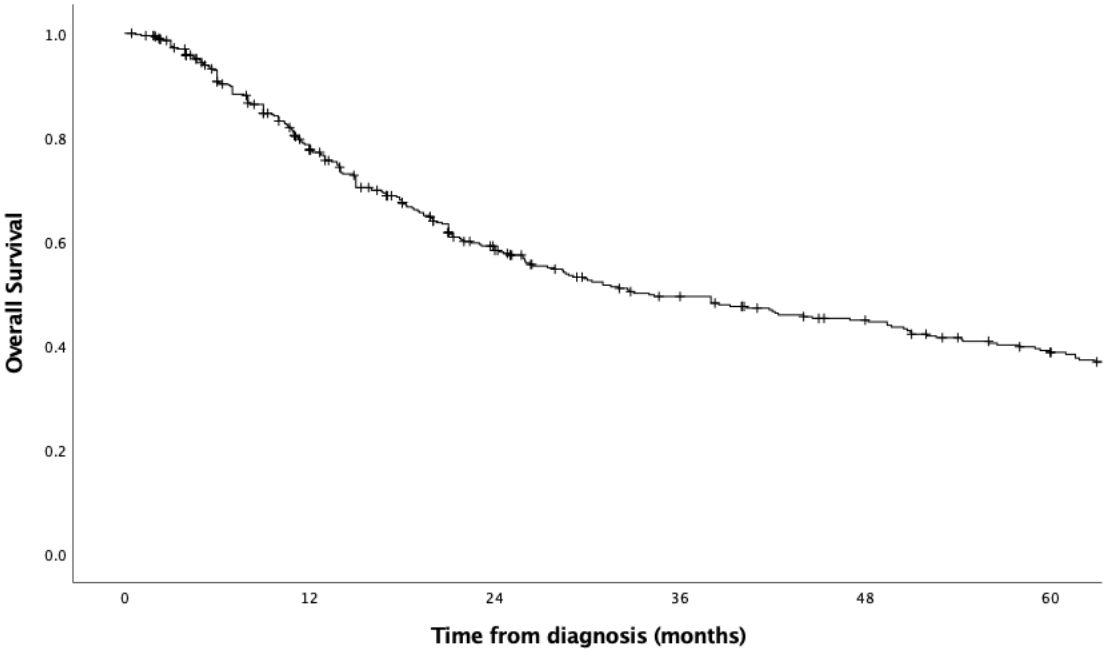
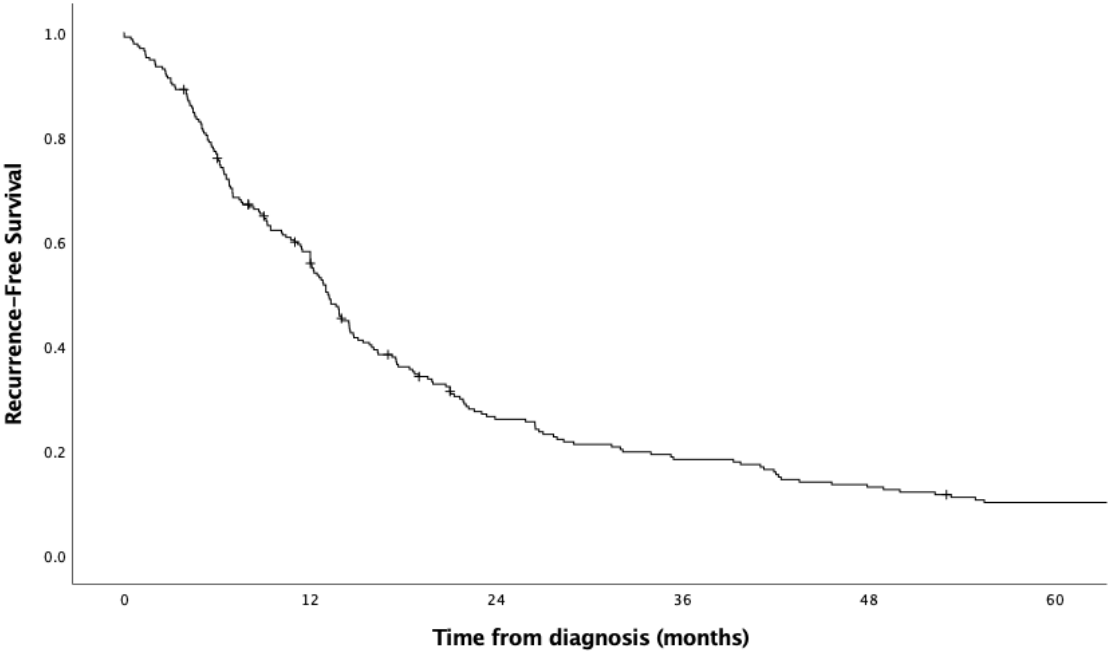


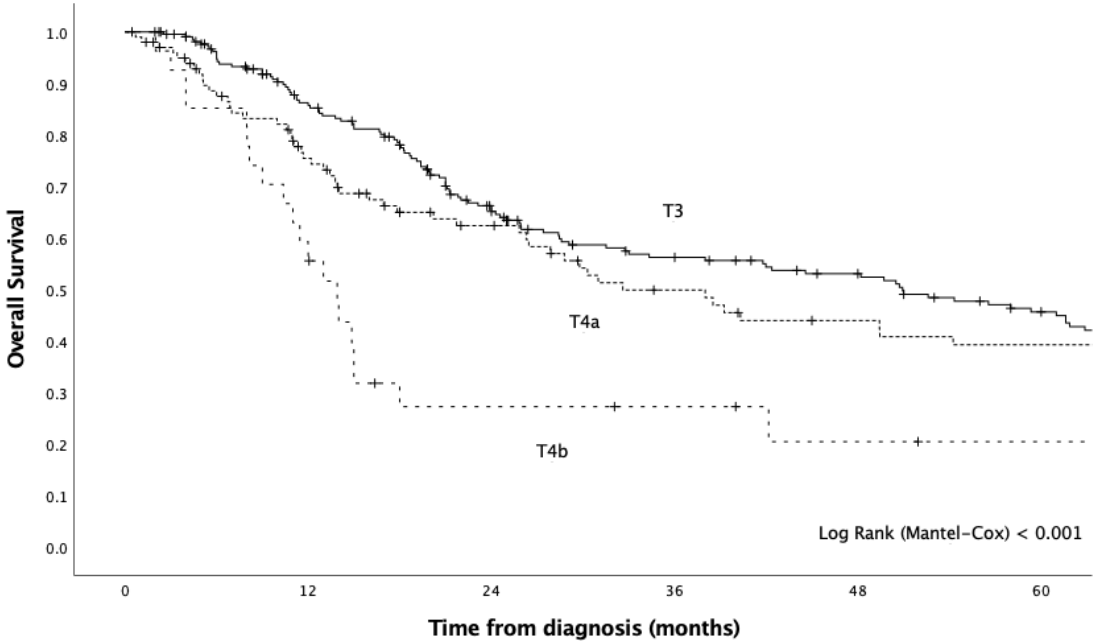
Number of events	0	92	164	193	207	225
Number at risk	436	304	200	156	133	106

Figure 1. Kaplan-Meier curve of overall survival.



Number of events	0	100	164	180	191	197
Number at risk	228	122	54	38	27	20

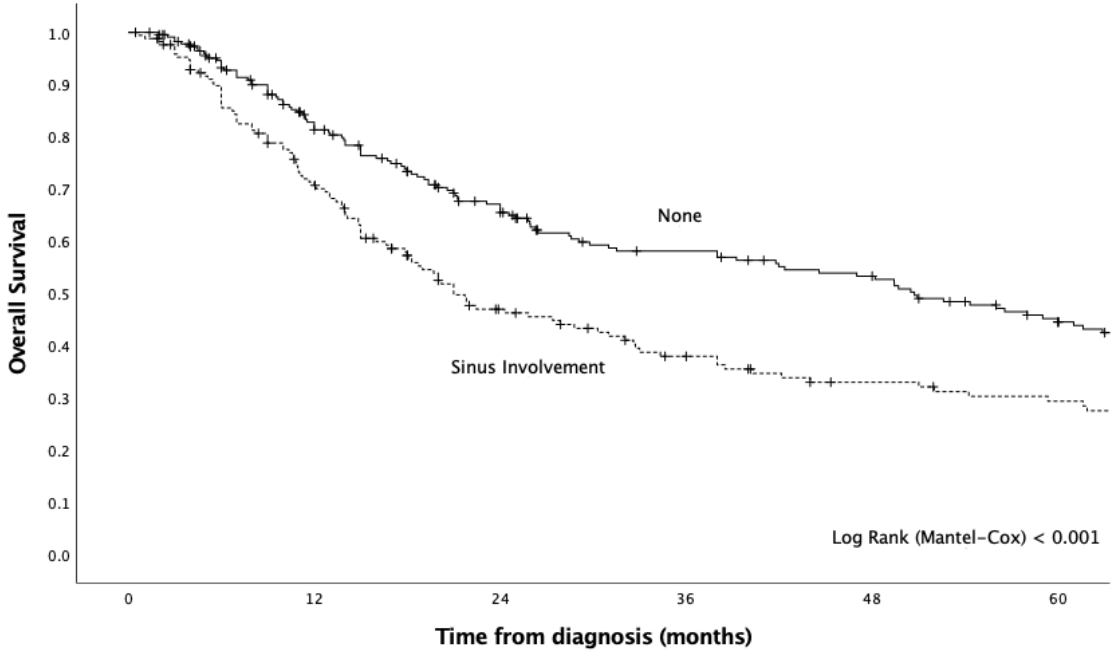
Figure 2. Kaplan-Meier curve of recurrence-free survival.



Number at Risk

T3	217	169	115	91	80	64
T4a	99	67	47	34	28	25
T4b	27	16	5	5	3	2

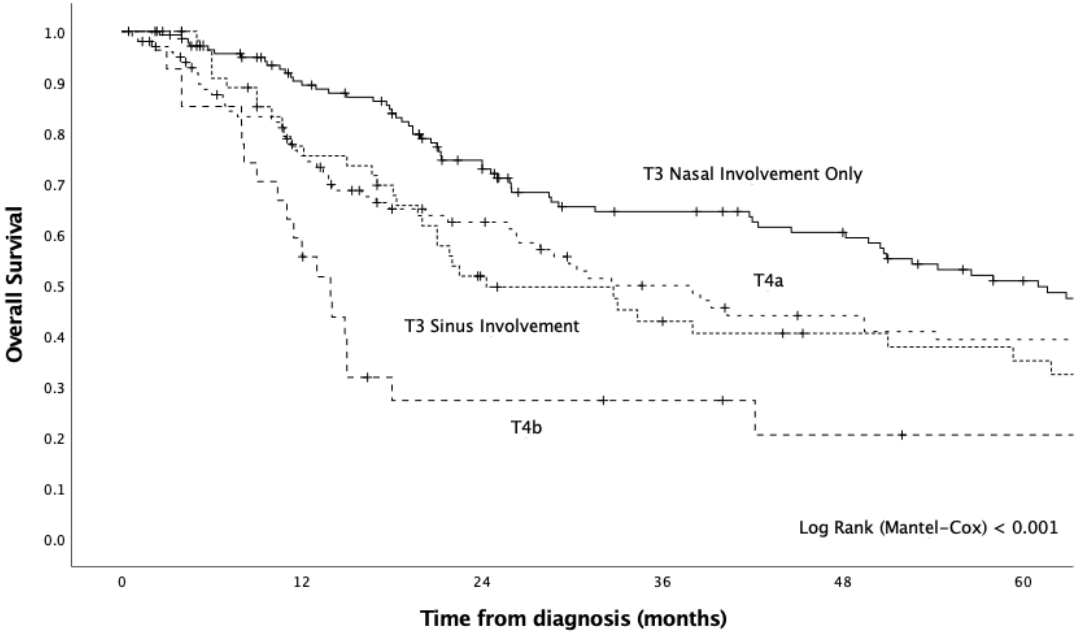
Figure 3. Kaplan-Meier curve of T Staging.



Number at Risk

Sinus Involvement	171	113	65	47	37	32
None	229	166	121	99	87	65

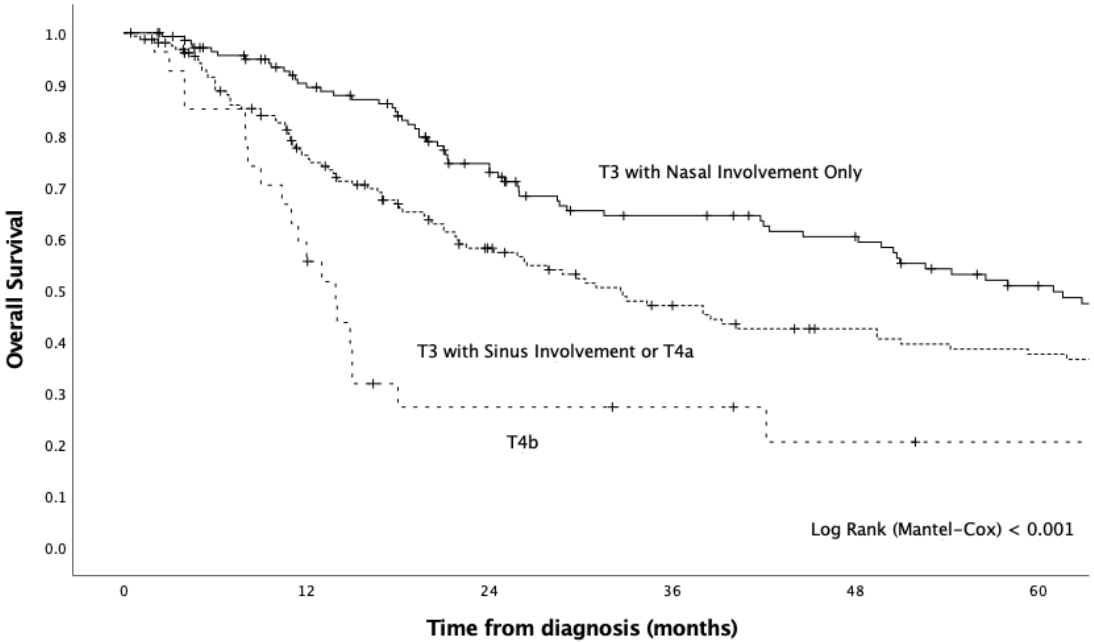
Figure 4. Kaplan-Meier curve of sinus (maxillary, frontal, ethmoid and/or sphenoid) involvement of the primary tumour.



Number at Risk

T3 Nasal Only	140	114	82	66	58	44
T3 with Sinus	56	40	24	18	15	13
T4a	99	67	47	34	28	25
T4b	27	15	6	5	3	2

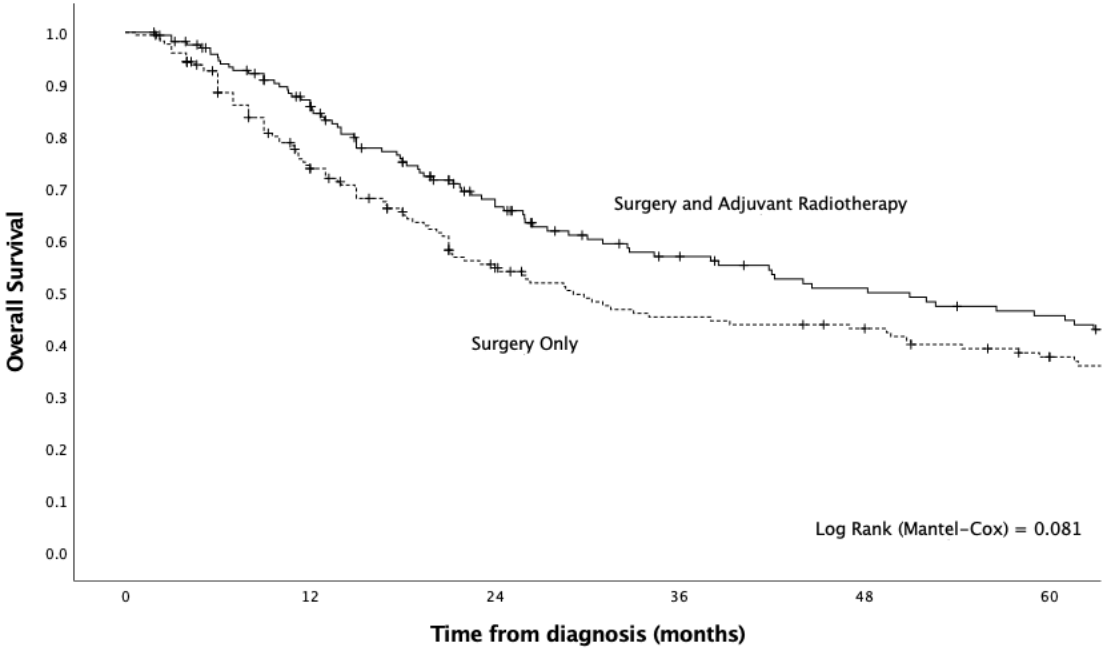
Figure 5. Kaplan-Meier curve of a modified T-staging system, where T3 has been stratified by sinus involvement.



Number at Risk

T3 Nasal Only	140	114	82	66	58	44
T3 with Sinus or T4a	156	107	71	52	43	38
T4b	27	15	6	5	3	2

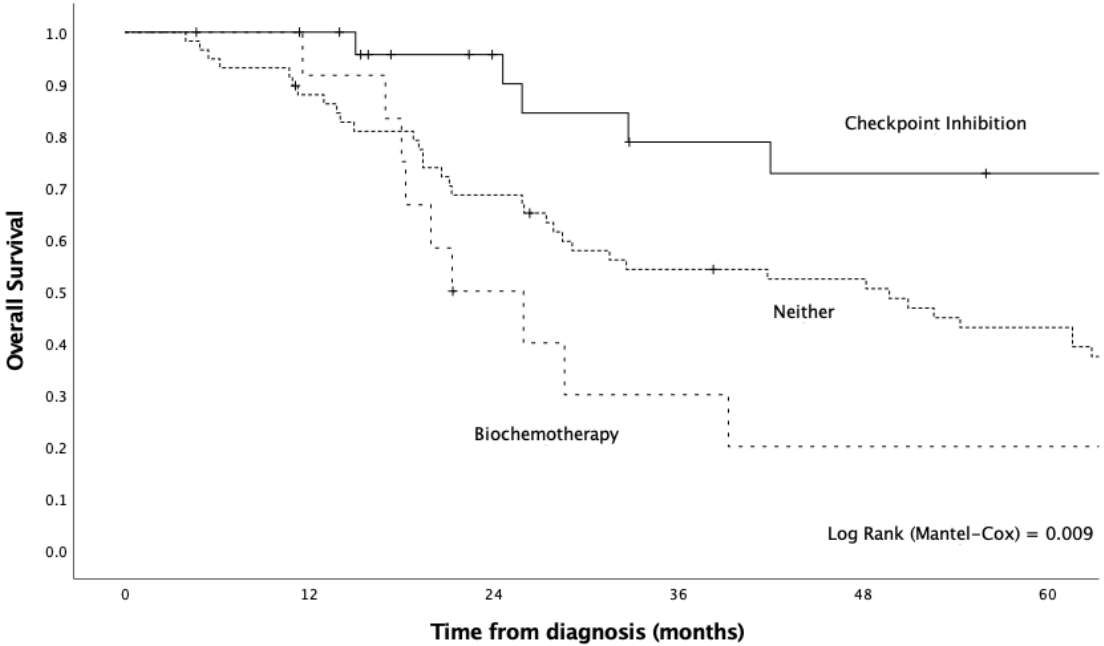
Figure 6. Kaplan-Meier curve of a modified T-staging system, where T3 with sinus involvement has been combined with T4a.



Number at Risk

Adjuvant RT	168	132	89	67	58	51
Surgery Only	176	119	78	62	56	44

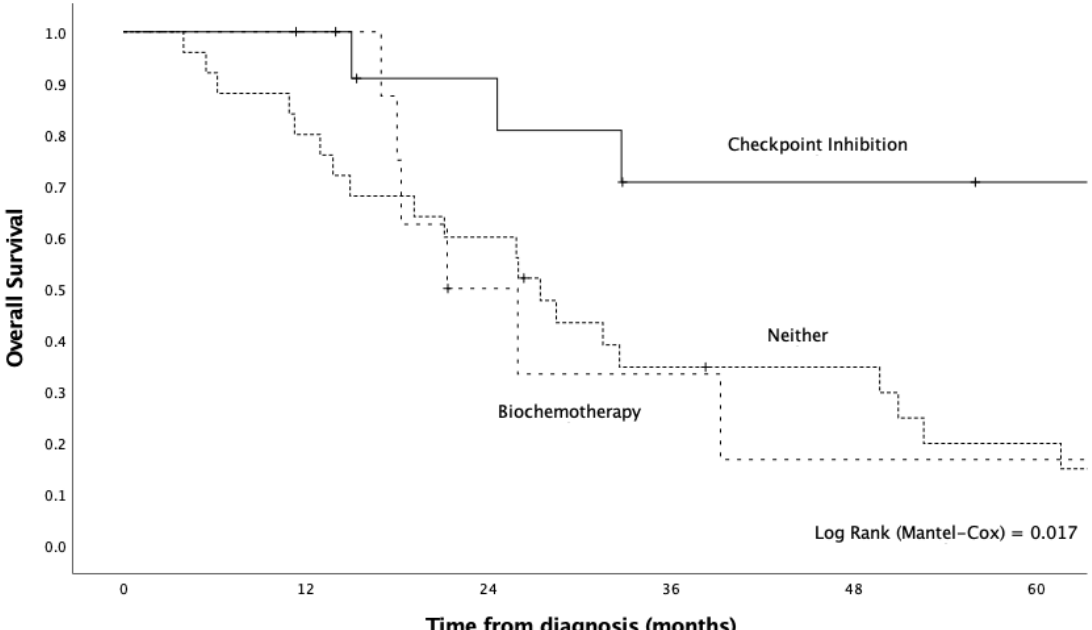
Figure 7. Kaplan-Meier curve of surgery only vs. surgery and adjuvant radiotherapy for the treatment of disease at presentation.



Number at Risk

Checkpoint Inhibition	25	24	17	13	12	11
Biochemotherapy	11	11	5	3	2	2
Neither	57	50	39	30	28	23

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.



Number at Risk

Checkpoint Inhibition	12	12	9	6	6	5
Biochemotherapy	7	7	3	2	1	1
Neither	24	20	15	8	7	4

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