Mutation status among patients with sinonasal mucosal melanoma and its impact on survival

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Background: Sinonasal mucosal melanoma (SNMM) comprises <1% of all melanomas and lacks well-characterised molecular markers. Our aim was to determine the frequencies of common mutations and examine their utility as molecular markers in a large series of primary SNMMs.

Methods: SNMM patients seen at our institution from August 1991 through July 2016 were identified. Genomic DNA was extracted from 66 formalin-fixed paraffin-embedded tumours and screened for mutations by direct sequencing. We investigated the association of mutations with clinicopathological features and survival outcomes.

Results: Overall, 41% (27 out of 66) of the SNMMs harboured mutations. *BRAF* and *KIT* mutations were identified in 8% (five patients) and 5% (three patients) of SNMMs, respectively, whereas *NRAS* mutations were detected in 30% (20 patients) of SNMMs. Mutation rates in these oncogenes were similar between SNMMs located in the paranasal sinuses and those in the nasal cavity (30% and 13%, respectively, $P = 0.09$). In a multivariate analysis, patients with negative margins had significantly better overall survival (hazard ratio 5.43, 95% confidence interval 1.44–21.85, $P = 0.01$) and disease-specific survival (hazard ratio 21.9, 95% confidence interval 3.71–180, $P = 0.0004$). The mutation status of the tumours showed no association with survival outcomes.

Conclusions: In SNNM, mutation status does not affect survival outcomes, but *NRAS* mutations are relatively frequent and could be targeted in this disease by *MEK* inhibitors.

Mucosal melanoma represents approximately 1.3% of all melanomas (Gal *et al*, 2011). While mucosal melanoma can arise from any mucosa-lined body surface, approximately half of all mucosal melanomas occur in the head and neck, most frequently in the sinonasal cavity (Lourenco *et al*, 2014; Sun *et al*, 2014). Sinonasal mucosal melanomas (SNMMs) account for ∼4% of sinonasal malignancies and <1% of all melanomas (Moreno *et al*, 2010; Gal *et al*, 2011; Lourenco *et al*, 2014).

Sun exposure is a well-known risk factor for cutaneous melanoma, but the risk factors for SNMM are less well defined (Spencer and Mehnert, 2016). Patients usually present later in life, with no obvious sex predilection (Spencer and Mehnert, 2016). The mitogen-activated protein kinase (MAPK) pathway has been shown to be important in the development of melanoma (Curtin *et al*, 2005a). In cutaneous melanoma, between 22 and 72% of cases have *BRAF* mutations, and 0 to 50% have *NRAS* mutations (Lee *et al*, 2011); however, molecular markers in mucosal melanoma are less well characterised. While recent studies suggest that *BRAF* inhibition has a promising effect in cutaneous melanoma, its role in SNMM has yet to be defined (Zebary *et al*, 2013a; Spagnolo *et al*, 2016).

SNMM is an aggressive tumour, and patients with SNMM often present with advanced disease (Ledderose and Leunig, 2015). Despite advances in treatment, survival is poor, with a 5-year survival rate of ∼20–30% (Moreno et al, 2010). Single-modality therapy with surgery is rarely adequate for this disease, particularly for SNMMs, in which anatomical and quality-of-life constraints make obtaining adequate margins very difficult and sometimes impossible (Samstein et al, 2016). Therefore, adjuvant therapy is a keystone in the treatment of SNMM. As more options arise for targeted therapy, the need to characterise molecular markers in SNMM has become increasingly important.

This study quantifies molecular features and attempts to identify molecular markers in SNMM. We also investigated the correlation of molecular features with clinicopathological features and survival outcomes to determine their prognostic utility in this disease.

MATERIALS AND METHODS

This retrospective review was approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center (Protocol RCR04-0636). We surveyed 170 consecutive patients seen at our institution from August 1991 through July 2016 with a pathologically confirmed diagnosis of head and neck mucosal melanoma involving the sinonasal cavity. The inclusion criteria for the analysis were: (1) pathologically confirmed mucosal melanoma; (2) sinonasal origin; (3) available outcome data; (4) available tissue for molecular analysis; and (5) adequate genetic material for analysis. Patient demographic features (age, sex, smoking status and alcohol intake), disease stage, tumour characteristics, treatment modalities used, pathological data (ulceration, perineural and lymphovascular invasion, bony invasion and number of mitotic figures, surgical margin status), and survival outcomes were collected. All staging was completed according to the *American Joint Committee on Cancer Staging Manual*, 7th edn (Edge et al, 2010).

The primary aim was the incidence of hotspot mutations. The secondary aim was the association between hotspot mutations and survival outcomes—overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS) and distant metastasis-free survival (DMFS)—and with clinicopathological features. The index date for survival outcomes for OS and DSS was set as the date of treatment initiation. DFS was defined as the time from the date of completion of primary treatment to the earliest evidence of disease recurrence. DMFS was defined as the time from the date of completion of primary treatment to the earliest evidence of distant metastasis.

Mutation analysis. Tumour cells were identified in regions with >20% nuclei. Genomic DNA was extracted from formalin-fixed paraffin-embedded tumours and subjected to PCR sequencing using a next-generation sequencing platform to screen for mutations in the coding sequences of 50 key signalling genes in melanoma (see Supplementary Table 1 for the full list of covered genes, exons and codons). The results of the next-generation sequencing were confirmed by a second independent PCR and sequencing reaction. The genomic reference sequence used was genome GRCh37/hg19. The sensitivity of the assay is related in part to depth of coverage, percentage of tumour cells with the mutation, and allelic frequency of the mutation. We determined the effective lower limit of detection of this assay (that is, analytical sensitivity) for single-nucleotide variations to be in the range of 5% (one mutant allele per 19 wild-type alleles) to 10% (one mutant allele per nine wild-type alleles) by considering the depth of coverage at a given base and the ability to confirm low-level mutations using independent conventional platforms. The variants detected by our assay were determined on the basis of both analytic findings, such as allelic frequency, and the currently available

Table 1. Demographic and clinical characteristics of patients with sinonasal mucosal melanoma (n = 66)	
Characteristics	**N (%)[a]**
Age (mean ± s.d.)	63 ± 13 years
Sex	
Female	33 (50%)
Male	33 (50%)
Smoking status	
Current	6 (9%)
Former	22 (33%)
Never	38 (58%)
Alcohol consumption	
Current	26 (39%)
Former	6 (9%)
Never	34 (52%)
Site	
Nasal cavity	53 (80%)
Paranasal sinuses	13 (20%)
T classification	
3	35 (53%)
4a	23 (35%)
4b	8 (12%)
N classification	
N0	59 (89%)
N+	7 (11%)
Mitosis rate	
<1	44 (66%)
⩾1	22 (33%)
Ulceration	
Absent	37 (56%)
Present	29 (44%)
Margins	
Positive	22 (33%)
Negative	44 (66%)
Treatment	
Surgery	26 (39%)
Surgery + radiation	28 (42%)
Surgery + chemotherapy	2 (3%)
Surgery + chemoradiation	2 (3%)
Chemotherapy	4 (6%)
Chemoradiation	2 (3%)
Follow-up time (mean ± s.d.)	40.1 ± 5.6 months
[a]Unless otherwise indicated.	

information in the curated reference databases COSMIC version 64 (Catalogue Of Somatic Mutations In Cancer, Wellcome Trust Sanger Institute, Hinxton, UK) and dbSNP version 137 (National Institute of Health, Bethesda, MD, USA).

Statistical analysis. Basic baseline descriptive statistics were generated. Continuous data were compared according to mutation status using the Student t-test, and categorical variables were compared according to mutation status using the χ^2-test. The Kaplan–Meier method was employed for all survival analyses. Survival curves were stratified according to the presence of mutations and compared using the log-rank test. Univariate and multivariate Cox proportional hazards models were used to compare survival outcomes according to mutation status and clinicopathological features. All statistical tests were two-tailed. Significance was defined by an alpha set to 0.05. All statistical testing was completed on SAS JMP Pro version 12.1.0 (SAS Institute, Cary, NC, USA).

RESULTS

Clinicopathological features. Sixty-six patients met all inclusion and exclusion criteria. Patient and tumour characteristics are

Table 2. Mutations identified in sinonasal mucosal melanoma

Patient #	Gene	Mutation	Age	Sex	Tumour epicentre	Exon	Nucleotide change	Amino acid change
1	TP53	Missense	44	Male	Maxillary sinus	5	c.404G>A	p.C135Y
2	TP53	Missense	62	Female	Nasal cavity	5	c.488A>G	p.Y163C
	KIT	Missense				13	c.1900C>T	p.R634W
	NOTCH1	Missense				4	c.742G>T	p.G248C
	NOTCH1	Missense				8	c.1393G>A	p.A465T
	NOTCH1	Frameshift				34	c.7494del	p.S2499
	PIK3R1	Missense				5	c.547G>A	p.A183T
	PIK3R1	Missense				15	c.1918G>T	p.G640W
	ERBB2	Missense				7	c.842C>T	p.S281F
3	NRAS	Missense	68	Male	Nasal cavity	2	c.182A>G	P.Q61R
4	NRAS	Missense	64	Male	Maxillary sinus	1	c.37G>C	p.G13R
5	NRAS	Missense	64	Female	Maxillary sinus	1	c.37G>C	p.G13R
6	NRAS	Missense	67	Male	Nasal cavity	1	c.37G>T	p.G13C
7	NRAS	Missense	51	Male	Nasal cavity	1	c.38G>c	p.G12A
8	NRAS	Missense	82	Male	Maxillary sinus	1	c.38G>c	p.G12A
9	NRAS	Missense	78	Male	Nasal cavity	1	c.38G>A	p.G13D
10	NRAS	Missense	65	Female	Nasal cavity	2	c.181C>A	p.Q61K
11	NRAS	Missense	75	Female	Nasal cavity	2	c.181C>A	p.Q61K
12	NRAS	Missense	62	Female	Maxillary sinus	2	c.181C>A	p.Q61K
13	NRAS	Missense	68	Female	Nasal cavity	2	c.181C>A	p.Q61K
14	NRAS	Missense	35	Male	Nasal cavity	2	c.181C>A	p.Q61K
15	NRAS	Missense	36	Female	Maxillary sinus	2	c.182A>G	P.Q61R
	FGFR1	Amplification					chr8:38271444-38315644	
16	NRAS	Missense	69	Male	Nasal cavity	2	c.182A>G	P.Q61R
17	NRAS	Missense	62	Female	Nasal cavity	2	c.182A>T	P.Q61L
18	NRAS	Missense	77	Female	Nasal cavity	1	c.34G>C	p.G12R
19	NRAS	Missense	60	Male	Maxillary sinus	1	c.35G>C	p.G12A
20	NRAS	Missense	63	Male	Nasal cavity	1	c.35G>T	p.G12V
21	NRAS	Missense	86	Male	Nasal cavity	1	c.37G>C	p.G13R
22	KIT	Missense	46	Female	Nasal cavity	2	c.146G>A	p.R49H
23	BRAF	Missense	37	Male	Nasal cavity	15	c.1799T>A	p.V600E
24	BRAF	Missense	55	Male	Nasal cavity	15	c.1799T>A	p.V600E
	NRAS	Missense				1	c.38G>A	p.G13D
25	BRAF	Missense	64	Male	Maxillary sinus	15	c.1799T>A	p.V600E
26	BRAF	Missense	56	Female	Nasal cavity	15	c.1799-1800GT>AA	p.V600K
	KIT					11	c.1632A>C	p.M541L
27	BRAF	Missense	55	Male	Nasal cavity	15	c.1781A>G	p.D594G

summarised in Table 1. There were 33 women and 33 men with a median age at diagnosis of 64 years (range 34–85 years). The tumour epicentre was located in the nasal cavity in 53 (80%) patients and in the paranasal sinuses in 13 patients (eight in the maxillary sinus, three in the sphenoid sinus, one in an ethmoid sinus and one in a frontal sinus). Thirty-five (53%) patients had T3 disease, 23 (35%) had T4a disease and eight (12%) had T4b disease. Nodal metastases were present in seven patients (11%). Surgery was the mainstay of treatment in 58 (88%) cases, and in 26 (39%) patients surgery was the only treatment modality. Adjuvant radiotherapy was administered in 30 (45%) patients, and four (6%) patients were treated with adjuvant chemoradiotherapy.

Mutation analysis. Of the 66 primary SNMMs analysed, 27 (41%) harboured at least one identified mutation, and 39 (60%) had no identified mutations. The most common mutation was *NRAS* mutation ($n = 20$, 30%, $P < 0.001$). Mutations in *BRAF*, *KIT* and *TP53* occurred in five (8%), three (5%) and two (3%) patients, respectively (Table 2). In 24 patients (89% of the patients with at least one mutation), mutations in *KIT*, *NRAS* and *BRAF* were mutually exclusive.

The *NRAS* mutations involved codons 12 (*G12A*, *G12R* and *G12V*), 13 (*G13R*, *G13C* and *G13D*) and 61 (*Q61K*, *Q61L*, and *Q61R*). Eleven of the *NRAS* mutations were located in exon 1. The three *KIT* mutations were missense; of those, one was the hotspot mutation *p.M541L* in exon 10 with simultaneous *BRAF V600K* mutation (patient 26, Table 2). One tumour harboured a *KIT* mutation in exon 13 simultaneously with *ERBB2*, *NOTCH1*, *PI3KR1* and *TP53* mutations. No mutations were observed in exon 17 of *KIT*. Among the five *BRAF* mutations, four were in codon 600 ($BRAF^{V600E}$ and $BRAF^{V600K}$), and one was in codon 594 (*D594G*). Both *TP53* mutations were in exon 5; interestingly, one of the patients with *TP53* mutation carried a germline polymorphism, but not mutation, of *KIT* (*c.1621A>C p.M541L*).

Association of mutations with clinicopathological features. The clinicopathological features of tumours with *NRAS, KIT, TP53* or *BRAF* mutations and tumours lacking these mutations are compared in Table 3. Tumours with these mutations were more likely to be located in the paranasal sinuses (30%), whereas the lesions without identified mutations were more often found in the nasal cavity (13%); however, the difference in location was not

Table 3. Association of identified mutations with clinicopathologic features

Characteristic	Mutations not identified (n = 39) N (%)[a]	Mutations identified (n = 27) N (%)[a]	P-value
Age (mean ± s.d.)	65.2 ± 12.6 years	61.3 ± 13.4 years	0.23
Sex			0.20
Female	17 (44%)	16 (59%)	
Male	22 (56%)	11 (41%)	
Smoking			0.14
Current/former	19 (49%)	9 (33%)	
Never	20 (51%)	18 (67%)	
Site			0.09
Nasal cavity	34 (87%)	8 (30%)	
Paranasal sinuses	5 (13%)	19 (70%)	
T classification			0.76
3	22 (56%)	13 (48%)	
4a	13 (33%)	10 (37%)	
4b	4 (10%)	4 (15%)	
N classification			0.36
N0	36 (92%)	23 (85%)	
N+	3 (8%)	4 (15%)	
Mitosis rate			0.01
<1	27 (69%)	10 (37%)	
⩾1	12 (31%)	17 (63%)	
Ulceration			0.59
Present	27 (69%)	17 (63%)	
Absent	12 (31%)	10 (37%)	
Cell morphology			0.43
Pagetoid	8 (21%)	6 (22%)	
Epithelioid	7 (18%)	7 (25%)	
Spindled	7 (18%)	9 (33%)	
Rhabdoid	8 (21%)	4 (15%)	
Undifferentiated (small cell)	13 (33%)	9 (33%)	
Bone invasion			0.35
Absent	33 (85%)	20 (74%)	
Present	6 (15%)	7 (26%)	
Treatment			0.88
Surgery	18 (46%)	12 (44%)	
Surgery and radiation	18 (46%)	12 (44%)	
Surgery and chemoradiation	3 (8%)	3 (12%)	

[a]Unless otherwise indicated.

statistically significant ($P = 0.09$). Mutated tumours had a significantly higher rate of mitosis compared with lesions without identified mutations (63% and 31% respectively, had mitosis rates of $\geqslant 1\,mm^{-2}$; $P = 0.01$). The distribution of SNMM cell morphological types (Thompson *et al*, 2003), including epithelioid, spindle, pleomorphic, rhabdoid pagetoid and undifferentiated (small) cells, was similar for patients with and without identified mutations. There were no differences between the mutation groups with respect to age at diagnosis, sex, smoking status, T classification, N classification or bone invasion. The occurrence rates of perineural and lymphovascular invasion were too low for analysis ($n = 2$ for both).

Association of mutations and clinicopathological features with survival outcomes. In the whole cohort, the 5-year OS rate was 39%, and the 5-year DSS rate was 54%. The 5-year OS rate was 43% in patients carrying a mutation and 37% in those without an identified mutation (log-rank $P = 0.55$; Figure 1A). The 5-year DSS rate was 54% for both mutation groups (log-rank $P = 0.91$; Figure 1B).

Recurrence occurred in 59 (89%) patients over the follow-up period; of these, 27 (40%) had distant metastases. The 5-year DFS was 24% in patients carrying a mutation and 11% for those without

an identified mutation (log-rank $P = 0.64$; Figure 1C). A subgroup analysis of patients with *NRAS* mutations showed no association of *NRAS* mutations with DFS or DMFS (log-rank $P = 0.31$ and $P = 0.57$, respectively). In patients without identified mutations there was a trend toward a higher 5-year distant metastasis rate compared with patients carrying *NRAS, KIT, TP53* or *BRAF* mutations (78% and 55%, respectively; log-rank $P = 0.07$; Figure 1D).

Univariate analysis comparing patients with and without detected mutations in their tumours showed no association of mutation status with either OS or DSS. To further assess the ability of mutation status to predict outcome in a more homogeneous population and to account for the potential impact of adjuvant treatment, we performed subgroup analyses of each of the following treatment groups: patients undergoing surgery alone ($n = 30$), patients undergoing postoperative radiotherapy ($n = 30$), and patients undergoing adjuvant chemoradiotherapy ($n = 6$). In all treatment groups, mutation status was not an independent predictor of OS or DSS (log-rank analysis, Supplementary Figure 1).

Patients with T3 disease had a significantly better prognosis than those with a T4a or T4b disease, with 5-year OS rates at 58%, 48% and 18%, respectively (log-rank $P = 0.02$, Figure 2A). Similarly, patients with negative margins had a better 5-year OS rate than patients with positive margins (54% and 27%, respectively; log-rank $P = 0.009$; Figure 2B). Of note, patients with tumours in the nasal cavity had a marginally better 5-year OS rate than those with tumours in the paranasal sinuses (48% and 22%, respectively; log-rank $P = 0.06$; Figure 2C). Multivariate Cox regression modelling of these data revealed that only margin status was a significant prognostic factor for OS (hazard ratio 5.43, 95% confidence interval 1.44–21.85, $P = 0.01$) and DSS (hazard ratio 21.9, 95% confidence interval 3.71–180, $P = 0.0004$). To control for margin status, we performed survival analyses separately in patients with positive and negative margins. This analysis revealed no difference in OS and DSS between patients with and without detected mutations in their tumours (Supplementary Figure 2).

DISCUSSION

In this study, we comprehensively screened primary SNMMs for over a hundred different mutations in more than 50 key genes in melanoma and found that *NRAS* mutations were prevalent (30%). In this retrospective, single-institution analysis, we did not find an association between mutation status and survival outcomes but did find that tumours with identified mutations had a higher mitosis rate.

Genomic aberrations are present in most melanomas (Hodis *et al*, 2012; Akbani *et al*, 2015). An increasing understanding of melanocyte biology and melanoma pathogenesis has led to the development of targeted therapies and the potential for major improvements in the care of patients with advanced melanoma. For now, large-scale genomic data in melanoma, derived mainly from cutaneous melanoma, focus on specific genes such as *NRAS* and its downstream mediator *BRAF* (Omholt *et al*, 2003). Targeting these pathways in patients with previously untreated melanoma with these mutations showed promising outcomes (Chapman *et al*, 2011). However, despite these breakthroughs, the prognosis of patients presenting with SNMM remains poor. Thus, we sought to characterise potential molecular markers in patients with these uncommon melanomas.

Published studies have reported slightly lower overall mutation rates in head and neck mucosal melanoma (10–25%) (Chraybi *et al*, 2013; Zebary *et al*, 2013b; Lyu *et al*, 2016; Ozturk Sari *et al*,
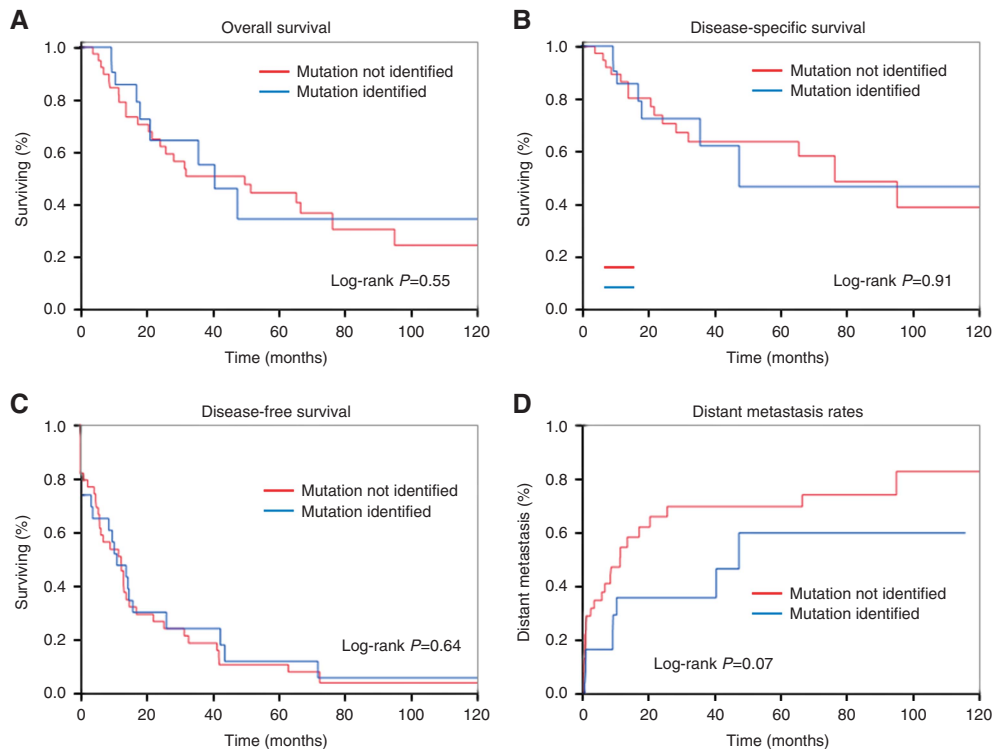
Figure 1. Comparison of survival outcomes in patients with sinonasal mucosal melanoma according to mutation status. (**A**) Ten-year overall survival, (**B**) disease-specific survival and (**C**) disease-free survival by mutation status and (**D**) 10-year distant metastasis rate calculated using the Kaplan–Meier analysis in patients with (blue line) and without (red line) identified mutations.

2017) than that in the current study (40%); however, there was a considerably similar distribution of specific mutation rates in these studies: *NRAS*, 14%–60%; *BRAF*, 0%–6%; and *KIT*, 3%–12% (Cohen *et al*, 2004; Beadling *et al*, 2008; Carvajal *et al*, 2011; Turri-Zanoni *et al*, 2013; Zebary *et al*, 2013b). The Cancer Genome Atlas and other large-scale genomic analysis efforts in melanoma have identified hotspot *NRAS* mutations, thought to be important drivers of oncogenesis, in 25–30% of cutaneous melanomas (Akbani *et al*, 2015; Krauthammer *et al*, 2015). Our data show a similar rate (30%) of *NRAS* mutations. However, in cutaneous melanoma, mutations at codon 61 (*Q61R* and *Q61K*) represent the two most common *NRAS* mutations. In the current study, only 40% of the patients carrying *NRAS* mutations had *Q61R* or *Q61K* mutations, whereas 55% of these patients had mutations in codons 12 (*G12V*, *G12A*, *G12R* and *G12D*) and 13 (*G13R*, *G13C* and *G13D*). These *NRAS* mutations at codons 12 and 13 are also prevalent in haematological malignancies (Ward *et al*, 2012). The different patterns of *NRAS* mutations in mucosal melanoma compared with cutaneous melanoma support an aetiology other than sun exposure. Another important risk factor in head and neck cancer is smoking. We found a trend towards a lower mutation rate in smokers; however, this difference did not reach significance.

The most common somatic event in cutaneous melanoma is mutation of the serine-threonine kinase *BRAF*, which is a component of the *RAS-RAF-MEK-MAPK* signalling pathway. Overall, point mutations in *BRAF* occur in 40–50% of melanomas (Curtin *et al*, 2005b). Over 90% of the mutations in *BRAF* result in substitution of the valine at position 600, resulting in activation of the downstream effectors of the *RAS-RAF-MEK-MAPK* pathway. Recently, a combination of anti-*BRAF* and anti-*MEK* agents have led to an increased response rate and longer duration of response in cutaneous melanoma patients (Larkin *et al*, 2014; Long *et al*, 2014). However, the use of these targeted agents is limited to the ∼40% of patients who have melanoma with a *BRAF^{V600}* mutation.

We identified *BRAF^{V600E}* and *BRAF^{V600K}* mutations in only four out of 66 SNMMs. This frequency is similar to the incidence of *BRAF* mutations in mucosal melanomas from other sites such as the vulva, vagina and anorectum (Omholt *et al*, 2003; Curtin *et al*, 2005b).

Most melanoma samples that harboured a hotspot mutation in *NRAS*, *KIT* or *BRAF* did so in a mutually exclusive fashion. The two exceptions harboured *BRAF^{V600}* mutations together with an oncogenic *NRAS* or *KIT* mutation. Two cases harboured a *TP53* missense mutation in exon 5. Interestingly, one patient presented with *NOTCH1*, *PI3KR1*, *TP53* and *KIT* mutations, all of which have been previously shown to have a role in melanoma oncogenesis (Liu *et al*, 2006).

We found a mutation in *KIT* in only three out of 66 SNMMs. Of those cases, two had additional identified mutation (patients 2 and 26, Table 2). *KIT* mutations are associated with chronic sun damage in cutaneous melanoma, which is not an aetiological risk factor in SNMMs (Curtin *et al*, 2005b). However, previous observations suggested that *KIT* is the most commonly mutated gene in mucosal melanoma, with up to 45% of vulvovaginal and anorectal melanomas carrying a mutation in *KIT* (Omholt *et al*, 2011; Schoenewolf *et al*, 2012). These findings suggest that *KIT* mutations differ between mucosal melanomas at different sites and are very rare in SNMMs.

We found a significantly higher mitosis rate in patients carrying an identified mutation. There also were trends toward a higher rate of mutations in tumours originating in the paranasal sinuses rather than the nasal cavity and worse prognosis in patients with disease originating from the sinuses compared with those with tumours originating from the nasal cavity. Our finding that mutation status, for all known mutations or for *NRAS* alone, did not affect survival in the setting of SNMM is in keeping with studies conducted before the availability of *MEK* inhibitors and immune checkpoint inhibitor antibodies (Ellerhorst *et al*, 2011). The high proportion
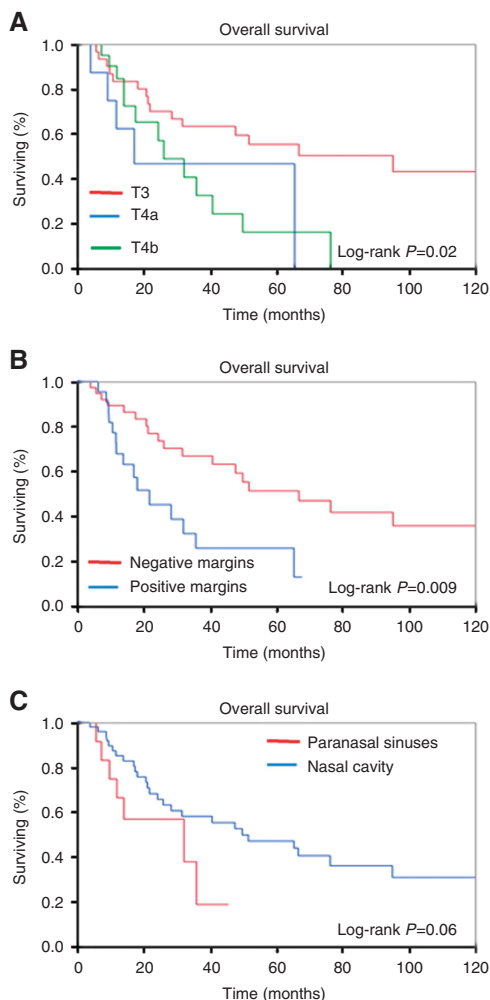
Figure 2. Independent risk factors in sinonasal mucosal melanoma. Kaplan–Meier curves of overall survival according to (**A**) T classification, (**B**) margin status and (**C**) tumour site. T classification and surgical margin status reliably distinguished between patients in each subgroup by risk for treatment failure ($P < 0.05$).

of *NRAS*-mutated tumours suggests that further studies investigating the use of *MEK* inhibitors, which have shown promising phase II results in cutaneous melanoma with *NRAS* mutations, may be worthwhile in SNMMs (Ascierto *et al*, 2013). A phase III study comparing the MEK inhibitor binimetinib with dacarbazine in patients with NRAS-mutant cutaneous melanoma showed longer progression-free survival in patients treated with binimetinib (Dummer, 2016). However, the adverse events profile of these agents, including cardiomyopathy, hypertension, coagulopathies and rash, makes them good candidates for a combined treatment regimen rather than single-agent therapy.

In the present study, we included only patients seen at a single tertiary cancer centre. Although mutation testing was done prospectively in patients with SNMM, data were collected and analysed retrospectively, which might limit our ability to control for patient comorbidities and different treatments administered. Also, matched non-tumour tissue was not tested, so the possibility of a detected mutation being a germline mutation cannot be completely ruled out. In our cohort, 24 patients had one mutation, two patients had two mutations, and one patient had eight mutations. Because of the low number of events, we could not analyse the correlation between the number of mutations and the outcome. However, our study represents the largest single-institution cohort to date of SNMM patients undergoing

characterisation of mutation status. The role of mutation status, particularly *NRAS* mutations in *G12* and *G13*, as a biomarker for response to *MEK* inhibition in SNMM needs to be addressed in future studies.

In conclusion, *NRAS*, *BRAF* and *KIT* mutations do not affect survival outcomes in SNMM. As *MEK* inhibitors have shown promise in the treatment of cutaneous melanoma, their prognostic impact in SNMM should be further investigated, especially in the relatively frequent cases with *NRAS* mutations.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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