**KIT, NRAS and BRAF mutations in sinonasal mucosal melanoma: a study of 56 cases**

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**Background:** Mucosal melanomas in the head and neck region are most frequently located in the nasal cavity and paranasal sinuses. Sinonasal mucosal melanoma (SNMM) comprises o 1% of all melanomas. The aim was to determine the KIT, NRAS and BRAF mutation frequencies in a large series of primary SNMMs.

**Methods:** Laser capture microdissection was used to isolate tumour cells from 56 formalin-fixed paraffin-embedded tumours. The tumour cells were screened for KIT, NRAS and BRAF mutations by direct sequencing.

**Results:** Overall, 21% (12 out of 56) of SNMMs harboured KIT, NRAS or BRAF mutations. Mutations in these oncogenes occurred in a mutually exclusive manner. Both KIT and BRAF mutations were identified at a similar frequency of 4% each (2 out of 56), whereas NRAS mutations were detected in 14% (8 out of 56) of the SNMMs. Four of the NRAS mutations were located in exon 1. Mutations in these oncogenes were significantly more common in melanomas located in the paranasal sinuses than in nasal cavity (P = 0.045). In a multivariate analysis, patients with melanomas in the nasal cavity had a significantly better overall survival than those with tumours in the paranasal sinuses (P = 0.027).

**Conclusion:** Our findings show that KIT and BRAF mutations, which are accessible for present targeted therapies, are only rarely present in SNMMs, whereas NRAS mutations seem to be relatively more frequent. The data show that majority of SNMMs harbour alterations in genes other than KIT, NRAS and BRAF.

Approximately 1–2% of all melanomas originate from the mucosal membranes in the digestive, respiratory and genitourinary tracts (Clifton et al, 2011; The National Board of Health and Welfare (1960–2009)). Mucosal melanomas in the head and neck region are most frequently located in the nasal cavity, followed by paranasal sinuses and oral cavity (Jethanamest et al, 2011). Primary sinonasal mucosal melanoma (SNMM), however, comprises <1% of all melanomas (Clifton et al, 2011), and conversely, SNMMs amount to only 1–9% of all malignant lesion of the nasal tract (Harbo et al, 1997; Norlander et al, 2003).

The incidence of SNMM in Sweden has increased significantly from 1960 through 2000, although not at the same pace as that of cutaneous melanoma (Jangard et al, 2013). For women, the incidence has doubled and for men it almost tripled comparing 1960–1964 vs 1995–2000. Patients with SNMM have a poor prognosis with 5-year survival rates of 20–28% (Lund et al, 2012; Jangard et al, 2013).

The mitogen-activated protein kinase and phosphatidylinositol-3 kinase-Akt pathways have critical roles in the pathogenesis of melanoma. Activation of these pathways in cutaneous and mucosal melanomas commonly occur through activating mutations in the BRAF, NRAS and KIT genes (Jovanovic et al, 2008; Omholt et al, 2011). However, mucosal melanomas have a distinct genetic background compared with cutaneous melanomas. For example, the frequency of BRAF mutation is significantly higher in melanoma arising in the trunk and skin without chronic sun damage than in mucosal melanomas (Curtin et al, 2005; Ellerhorst et al, 2011; Lee et al, 2011). On the other hand, NRAS mutations are frequently detected in melanomas located in extremities and skin with chronic sun damage (Ellerhorst et al, 2011; Lee et al,
Tumour cells were microdissected from sections by laser capture microdissection (LCM) using the Arcturus PixCell LCM System (Arcturus Engineering, Mountain View, CA, USA) according to the manufacturer’s recommendations. Samples were incubated overnight with protease K-enriched digestion buffer (PicoPure DNA Extraction Kit, Arcturus Engineering) to extract the DNA from the dissected cells. Protease K was then inactivated by heating samples at 95 °C for 10 min.

**Mutation analysis.** Genomic DNA was subjected to first and nested PCR to amplify BRAF (exon 15), NRAS (exons 1 and 2) and KIT (exons 11, 13 and 17) genes. In the first PCR, the DNA was amplified in a 10 μl mixture reaction containing 2.5 mM deoxynucleotide triphosphate, 5 μM primer Taq DNA polymerase (Invitrogen, Carlsbad, CA, USA), 50 pmol μl⁻¹ of each primer, 10 × PCR buffer, 50 mM MgCl₂ and 10 μg μl⁻¹ bovine serum albumin. Two microlitres of the first PCR reaction was used as DNA template for the nested PCR. The DNA was extracted and purified from agarose gels by using QIAquick Gel Extraction Kit (Qiagen, Valencia, CA, USA). Sequencing reactions were performed in a final volume of 20 μl using BigDye Terminator V1.1 Cycle Sequencing kit (Applied Biosystems, Foster City, CA, USA). The sequencing products were purified by ethanol precipitation, and automated DNA sequencing was performed by ABI PRISM3130xl Genetic Analyzer (Applied Biosystems). All mutations were confirmed by a second independent PCR and sequencing reaction. The primers used for amplification and sequencing are described in Supplementary Table 1.

**Statistical analysis.** Fisher’s exact test was used to correlate the mutation status with clinicopathological features such as gender, ulceration, anatomical site and pigmentation. Age at diagnosis was compared between the mutated and wild-type group using Wilcoxon rank-sum test. Overall survival was estimated from the date of diagnosis to the date of death or last follow-up (1 November 2012). Patients who were alive at the end of the study were censored. Survival data were available for all patients. Multivariate Cox regression model, Log-rank test and Kaplan–Meier graphs were used to assess the association of anatomical site with overall survival. All P-values were two-sided. P-values < 0.05 were considered statistically significant.

**RESULTS**

**Clinicopathological characteristics.** Patient and tumour characteristics are listed in Table 1. Overall, there were 35 females and 21 males with a median age at diagnosis of 76 years. Thirty-four tumours were located in the nasal cavity and 22 in the paranasal sinuses (10 in the maxillary sinuses, 6 in the ethmoid sinuses and 6 tumours invaded the surrounding structures: 4 involved the orbit; one the skull base and another one spread to the retromaxillary infratemporal fossa).

**Mutation analysis.** Of the 56 primary SNMMs analysed, 12 (21%) harboured KIT, NRAS or BRAF mutations and 44 (79%) were wild type. Mutations in KIT, NRAS and BRAF occurred in a mutually exclusive manner. The difference between KIT, NRAS and BRAF mutation frequencies in SNMMs was borderline significant (P = 0.058). KIT mutations were detected in 2 of the 56 SNMMs (4%). Both tumours with KIT mutations contained the hotspot mutation L576P in exon 11 (Table 2). No mutations were observed in exons 13 and 17. In our previous study, we identified a much higher frequency of KIT mutations in vulvar melanomas, with mutations in 8 of 23 tumours (35%; Omholt et al, 2011). Thus, in our material the difference between the updated results on KIT mutation frequencies in SNMMs was borderline significant (P = 0.011).
frequency in SNMMs and that previously presented for vulvar melanomas is statistically significant ($P = 0.001$).

NRAS mutations were identified in 8 (14%) and BRAF mutations in 2 (4%) of the 56 SNMMs. Among the identified NRAS mutations, four were found in exon 1 (G12C, G12D, G12A and G13D) and four in exon 2 (Q61K, Q61R and Q61H ($n = 2$)). The BRAF mutations consisted of one V600E and one V600K change. Both BRAF mutated tumours were located in maxillary sinuses (Table 2).

**Association of mutations with clinicopathological features.** As the number of mutations identified was small, we compared the clinicopathological features between tumours with KIT, NRAS or BRAF mutations and those lacking these mutations. Tumours with mutations were more likely to be located in the paranasal sinuses, whereas the wild-type lesions were more often found in the nasal cavity and the difference was statistically significant ($P = 0.045$, Table 3). There was no difference between the mutated and wild-type group with respect to age at diagnosis, gender, ulceration and tumour pigmentation.

**Survival.** In univariate analysis, the age, anatomical site and clinical stage were significantly associated with overall survival. Patients with melanoma in the nasal cavity had a significantly better prognosis than those with a tumour in the paranasal sinuses (median survival, 39 vs 16 months; Log-rank $P = 0.027$; Figure 1). This effect remained significant in a multivariate analysis after adjusting for age at diagnosis, gender, ulceration, pigmentation and clinical stage ($P = 0.001$). The mutation status of the tumours showed no association with the overall survival.

**Discussion**

Mutational data on SNMM are rare and there are only a few published reports with limited number of tumours (listed in Table 4). In this study, which is the largest of its kind, to our knowledge, we screened primary SNMM for mutations in some of the most commonly mutated oncogenes in cutaneous melanoma. We identified KIT, NRAS and BRAF mutations in 4%, 14% and 4% of tumours, respectively. The finding of KIT mutations in only 2 of 56 SNMMs suggests that KIT mutations differ between mucosal melanomas at different sites, and that they are very rare in this subtype of mucosal melanomas. Altogether, the present results and those of our previous study on mucosal melanomas from several different sites show that the KIT mutation frequency in SNMM is

| Table 1. Patient and tumour characteristics |
|-------------------------------------------|
| Characteristics                          |
| Total $n = 56$                           |
|                                           |
| **Age at diagnosis, year**               |
| Median                                    |
| 76                                       |
| Mean                                     |
| 74                                       |
| Range                                    |
| 52–97                                    |
| **Gender, $n$ (%)**                      |
| Male                                      |
| 21 (37.5)                                |
| Female                                   |
| 35 (62.5)                                |
| **Anatomical site, $n$ (%)**             |
| Nasal cavity                             |
| 34 (60.7)                                |
| Paranasal sinus                          |
| 22 (39.3)                                |
| **Ulceration, $n$ (%)**                  |
| Present                                  |
| 34 (60.7)                                |
| Absent                                   |
| 14 (25.0)                                |
| Data missing                             |
| 8 (14.3)                                 |
| **Pigmentation, $n$ (%)**                |
| Present                                  |
| 23 (41.1)                                |
| Absent                                   |
| 25 (44.6)                                |
| Data missing                             |
| 8 (14.3)                                 |
| **Ballantyne staging**                   |
| I                                        |
| 52 (92.8)                                |
| II                                       |
| 1 (1.8)                                  |
| III                                      |
| 1 (1.8)                                  |
| Data missing                             |
| 2 (3.6)                                  |
| **Median survival, month (range)**       |
| 32 (2–230)                               |
| **Alive, $n$**                           |
| 10                                       |
| **Dead, $n$**                            |
| 46                                       |
| *Last updated on 1 November, 2012.*      |

| Table 2. Summary of mutations identified in primary SNMM ($n = 56$) |
|---------------------------------------------------------------|
| **Case** | Gender | Age | Anatomical site | Gene | Exon | Nucleotide change | Amino-acid change |
|----------|--------|-----|----------------|------|------|-------------------|-------------------|
| 1        | F      | 63  | Nasal cavity   | KIT  | 11   | c.1727T>C         | p.L576P           |
| 2        | M      | 65  | Maxillary sinus| KIT  | 11   | c.1727T>C         | p.L576P           |
| 3        | M      | 88  | Maxillary sinus| NRAS | 1    | c.34G>T           | p.G12C            |
| 4        | F      | 66  | Maxillary sinus| NRAS | 1    | c.35G>A           | p.G12D            |
| 5        | M      | 78  | Ethmoid sinus  | NRAS | 1    | c.35G>C           | p.G12A            |
| 6        | F      | 97  | Nasal cavity   | NRAS | 1    | c.38G>A           | p.G13D            |
| 7        | M      | 70  | Nasal cavity   | NRAS | 2    | c.181C>A          | p.Q61K            |
| 8        | F      | 58  | Maxillary sinus| NRAS | 2    | c.182A>G          | p.Q61R            |
| 9        | M      | 68  | Maxillary sinus| NRAS | 2    | c.183A>C          | p.Q61H            |
| 10       | F      | 82  | Nasal cavity   | NRAS | 2    | c.183A>C          | p.Q61H            |
| 11       | F      | 80  | Maxillary sinus| BRAF | 15   | c.1799T>A         | p.V600E           |
| 12       | F      | 52  | Maxillary sinus| BRAF | 15   | c.1798G>T>AA      | p.V600K           |

*Abbreviations: F = female; M = male; SNMM = sinonasal mucosal melanoma.*
Figure 1. Overall survival of patients with SNMM located in the nasal cavity and paranasal sinuses.

Table 3. Association of mutation status with clinical features in primary SNMMs (n = 56)

|                      | Mutateda | Wild typeb | P-value |
|----------------------|----------|------------|---------|
| **Median age, year (range)** | n = 12   | n = 44     |         |
| Male                 | 69 (52–97) | 76 (52–93) | 0.347   |
| Female               | 7 (58.3)  | 28 (63.6)  |         |
| **Anatomical site, n (%)** |          |            |         |
| Nasal cavity         | 4 (33.3)  | 30 (68.2)  | 0.045   |
| Paranasal sinus      | 8 (66.7)  | 14 (31.8)  |         |
| **Ulceration, n (%)** |          |            |         |
| Present              | 6 (50.0)  | 28 (63.6)  |         |
| Absent               | 1 (8.3)   | 13 (29.6)  |         |
| Data missing         | 5 (41.7)  | 3 (6.8)    |         |
| **Pigmentation, n (%)** |          |            | 0.189   |
| Present              | 3 (25.0)  | 20 (45.4)  |         |
| Absent               | 8 (66.7)  | 19 (43.2)  |         |
| Data missing         | 1 (8.3)   | 5 (11.4)   |         |

Abbreviation: SNMM = sinonasal mucosal melanoma.

<sup>a</sup> Mutated in KIT, NRAS or BRAF.

<sup>b</sup> Wild type in KIT, NRAS and BRAF.

In contrast to KIT mutations, the frequency of BRAF mutations is generally low in mucosal melanomas and does not seem to vary significantly between different sites (Omholt et al, 2011). In the current study, BRAF mutations were identified in 4% of SNMMs, which is similar to that detected in mucosal melanomas from other sites such as the vulva, vagina and anorectum (Curtin et al, 2006; Omholt et al, 2011).

The frequency of NRAS mutations that we identified in SNMM (14%) seem to be similar to that seen in cutaneous melanomas (Omholt et al, 2003; Edlundh-Rose et al, 2006; Lee et al, 2011). Interestingly, however, the types of NRAS mutations that we detected in SNMM differ from the types that predominate in cutaneous melanomas. In cutaneous melanomas, substitutions of glutamine for either arginine or lysine at codon 61 (Q61R and Q61K) represent the two most common NRAS mutations (Hocker and Tsao, 2007). In the current study, only two of eight NRAS-mutated tumours contained either of these mutations, whereas two had other alterations at codon 61 and four tumours contained mutations at codon 12 or 13 in exon 1. This indicates that NRAS mutations in mucosal melanomas, as opposed to cutaneous melanomas, are present in exon 1 and 2 with similar frequencies (Omholt et al, 2011; Turri-Zanoni et al, 2012). The NRAS mutations at codon 12 and 13 also predominate in other malignancies such as haematological cancers (Ward et al, 2012). The different pattern of NRAS mutations in mucosal melanoma, compared with cutaneous melanoma, possibly indicate an aetiology hitherto unknown but different from UV-radiation.

Interestingly, we found that mucosal melanomas located in the sinuses have a higher frequency of KIT, NRAS or BRAF mutations than those located in the nasal cavity. We also found that patients with disease emerging from the sinuses have a worse prognosis compared with those with tumours originating from the nasal cavity. This has also been observed in other studies (Liéton et al, 2010; Jethanamest et al, 2011). In the current study, the poor prognosis might be the result of more advanced tumour stage because in six cases the paranasal tumours invaded the surrounding structures. It remains to be addressed whether the adverse prognosis is associated with more aggressive biology and whether this is linked to the presence of oncogene mutations. Here we found no difference in overall survival between patients with mutated melanomas and those with wild-type melanomas.

Table 4. Summary of KIT, NRAS and BRAF mutations in SNMM

| Reference          | SNMM | KIT | NRAS | BRAF |
|--------------------|------|-----|------|------|
| Cohen et al (2004) | 17   | —   | —    | 5.9% (1/17) |
| Beadling et al (2008) | 29  | 8.4% (3/36)<sup>a</sup> | b | 0.0% (0/29) |
| Carvajal et al (2011) | 5  | 40.0% (2/5) | 60.0% (3/5) | 0.0% (0/5) |
| Schoeneewolf et al (2012) | 12 | 0.0% (0/12) | — | — |
| Turri-Zanoni et al (2012) | 32 | 12.5% (4/32) | 21.9% (7/32) | 3.1% (1/32) |
| Current study      | 56   | 3.6% (2/56) | 14.3% (8/56) | 3.6% (2/56) |
| Total              | 151  | 7.8% (11/141) | 19.3% (18/93) | 2.9% (4/139) |

Abbreviation: SNMM = sinonasal mucosal melanoma; ‘—’ = not determined.

<sup>a</sup> 29 melanomas were sinonasal and 7 were oral melanomas.

<sup>b</sup> The NRAS mutation frequency was not specified by anatomical site.

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however, the number of mutations identified are too small, which can skew the results. In our previous study, we found that KIT mutations as well as NRAS mutations associated with poor survival in univariate but not in multivariate analysis (Omholt et al, 2011). In contrast to our results, a recent Chinese study showed that KIT mutations adversely affected survival (Kong et al, 2011); however, in this report mucosal melanomas were combined with cutaneous melanomas and a multivariate analysis was not performed.

The frequencies of KIT and BRAF mutations in SNMMs suggest that only a minority of patients with SNMM may benefit from treatment with KIT and BRAF inhibitors. The higher proportion of NRAS-mutated tumours suggest that it may be worthwhile to perform studies using MEK inhibitors, which have shown promising phase II results in cutaneous melanoma with NRAS mutations (Ascierto et al, 2013). It would be intriguing to investigate whether tumours with codon 12–13 activating mutations have similar therapeutic outcome as cutaneous melanomas with codon 61 mutations. Mutation analysis might yield positive results particularly in tumours from parapharyngeal sinuses, as our results indicate that tumours from these areas more probably harbour mutations in KIT, NRAS or BRAF than the tumours from the nasal cavity. Still, a majority of SNMMs has other unknown underlying oncogenic driver mutations that need to be addressed in future studies. Very recently, a high frequency of somatic mutations have been discovered in the promoter of telomerase reverse transcriptase (TERT) in cutaneous melanoma, resulting in increased transcriptional activity at the TERT promoter that might act as driver mutations (Horn et al, 2013; Huang et al, 2013). Presence of mutations in TERT promoter is still waiting to be determined in mucosal melanomas.

In conclusion, our results show that KIT, NRAS and BRAF mutations occur at low frequencies in SNMM, and confirm our recent findings that the frequency of KIT in mucosal melanoma mutations vary significantly between different anatomical sites.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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