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Genetic aberrations in primary esophageal melanomas: molecular analysis of *c-KIT*, *PDGFR, KRAS, NRAS* and *BRAF* in a series of 10 cases

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We present a series of 10 primary esophageal melanomas of Caucasian patients characterized clinicopathologically and on the molecular level. Mutation analysis for *c-Kit* (exons 9, 11, 13 and 17), *PDGFR* (exons 12, 14 and 18), *NRAS* and *KRAS* were determined using PCR and direct sequencing. Analysis of the V600E mutation of *BRAF* was performed using mutation-specific PCR. Expression of c-Kit and PDGFR-A was additionally determined using immunohistochemistry. One tumor harbored a missense mutation in the *c-Kit* (p.F504L) and in the *KRAS* gene (p.G12S). A different *c-Kit* mutation (c.1507_1508 ins TTGCCT) was detected in another case. A third case had a V600E *BRAF* mutation. Using immunohistochemistry, c-Kit expression could be detected in all cases. The two cases with *c-Kit* mutations showed high c-Kit expression. None of the tumors showed a *PDGFR* mutation or expression or a *NRAS* mutation. We conclude that molecular analysis can identify targets for a specific therapy such as tyrosin kinase inhibitors as additional treatment option in these highly malignant tumors.
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Primary esophageal melanoma is an extremely rare disease accounting for 0.2% of all esophageal neoplasms and <0.05% of all melanoma subtypes.[1–3] Melanoma is a highly aggressive tumor, and for esophageal melanoma, as for mucosal melanoma in general,[4] prognosis is bad even if the disease is detected in early stages with small tumor sizes. Surgical resection is the preferential method of treatment in operable patients.[5] However, in most cases the tumor has to be regarded as systemic disease because of a very early lymphatic or hematogenic spread. Therefore, adjuvant treatment for primary esophageal melanoma may improve patient's prognosis. Unfortunately, chemotherapeutic treatment even in a combination therapy (chemoimmunotherapy or radiochemotherapy) shows response rates of only 20%.[2] In the advent of targeted therapies, a number of new drugs have been developed that direct toward specific molecules in signaling pathways essential for carcinogenesis and that may also provide a therapeutic option in melanoma.[6,7] In both cutaneous and noncutaneous melanomas, various genetic aberrations occur and among them c-Kit, RAS-isoform and *BRAF* alterations are found at various frequencies.[8–10] However, molecular information about primary esophageal melanoma is scarce because of its rarity, and recent reports represent only small series or case reports with analysis of single or few molecular aberrations: most recently, Terada *et al*[11] have reported two cases from Japan where a *PDGFR-A* and a *c-KIT* mutation analysis was performed, without demonstrating a *PDGFR-A* and a *c-KIT mutation* in these tumors. Sekine *et al*[12] have described a larger series of 16 esophageal melanomas from Japan as well. They could detect six cases with

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NRAS mutations, one *BRAF* mutation and one *c-KIT* mutation.

Out of a large collective of patients who underwent esophagectomy during the last 15 years in the surgical department of the Klinikum Rechts der Isar, Technische Universität München, we selected all cases of Caucasian patients with primary esophageal melanomas from whom formalin-fixed, paraffin-embedded tumor tissue was available. The histological slides were reviewed and a comprehensive molecular analysis of *c-Kit*, *PDGFRA*, *KRAS*, *N-RAS* and *BRAF* was performed. The expression of c-Kit and PDGFRA was additionally investigated using immunohistochemistry. The results were compared with clinicopathological parameters and patient's outcome.

Patients and methods

Patients

Formalin-fixed and paraffin-embedded tumor tissue was available from 10 cases. Diagnosis of primary esophageal melanoma was confirmed by endoscopic biopsy in all cases. Metastatic disease of cutaneous or mucosal melanoma was excluded by dermatological consultation and patient history. Overall survival was calculated from the day of surgery.

Experimental Methods

For molecular analysis, DNA was isolated from formalin-fixed and paraffin-embedded tumor tissue. Mutation analysis was done using PCR and direct sequencing.

Primers and PCR conditions for the *c-Kit* gene (exons 9, 11, 13 and 17) were as described before.[13] Primers for *PDGFRA* analysis were: exon 12, 5′-CT CTGGTGCACTGGGACTTT-3′ (forward) and 5′-GGA GGTTACCCCATGGGACT-3′ (reverse); exon 14, 5′-GAGAACAAGAAGATGGTAGCTCA-3′ (forward) and 5′-TTCACAACCACATGTGTCCA-3′ (reverse); and exon 18, 5′-CATTTCTTCCTTTTCCATGCA-3′ (forward) and 5′-TGTGGGAAGTGTGGACGTAC-3′ (reverse).

Primers for *kRAS* (exon 2, encompassing the most frequently altered codons 12 and 13) were 5′-GGT GGAGTATTTGATAGTGTATTAACC-3′ (forward) and 5′-CCTCTATTGTTGGATCATATTCG-3′ (reverse). Primers for *N-RAS* were 5′-GATGTGGCTCGCCAAT TAAC-3′ (forward) and 5′-CACTGGGCCTCACCTC TATG-3′ (reverse) for exon 2 and 5′-CACCCCCAG GATTCTTACAG-3′ (forward) and 5′-TCCGCAAAT CACTTGCTATT-3′ (reverse) for exon 3.

PCR reactions were run as 25 μl reaction mixtures consisting of 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 mM $MgCl_2$, 0.01% gelatin, 200 mM dNTP and 0.4 mM of each primer. After an initial denaturation at 95 °C for 10 min, 40 cycles were performed of 30 s at 94 °C, 30 s at 57 °C (*PDGFRA*, exons 12, 14 and 18), at 60 °C (*KRAS*, exon 2) or at 55 °C (*NRAS*, exons 2 and 3) and 30 s at 72 °C, followed by a final extension of 7 min at 72 °C. DNA sequencing of the PCR products was performed by cycle sequencing with fluorescent-labeled dye terminators and separation with an automated sequencing system (Genetic analyzer 2100, Applied Biosystems). For the analysis of *BRAF*, a mutation-specific PCR for the V600E mutation was performed according to Loughrey *et al*.[14] All detected mutations were independently confirmed starting with a new PCR reaction.

For immunohistochemical analysis, paraffin sections were immunostained on an automated immunostainer (Benchmark, Ventana Medical Systems, Tucson, AZ, USA) using the polyclonal rabbit antibodies anti-CD117 (anti-human CKIT A 4502, Dako, Glostrup, Denmark) and anti-PDGFR-A (anti-human PDGFR-A 3164, Cell Signaling Technologies, Beverly, MA, USA). The immunohistochemical protein expression was evaluated semiquantitatively based on the intensity of membranous or membranous and cytoplasmic staining ($+1$, $+2$, $+3$) and the percentage of positive tumor cells ($<5\%$, 5–50%, 50–95% and $>95\%$) according to Torres-Cabala *et al*.[15]

Results

Clinicopathological Parameters

There were three female and seven male patients. The mean age was 65 years (range 55–75). The mean overall survival was 10 months (95% confidential interval 0.0–27.7; range 0.8 months–17 months). Except for one patient, all patients died of the disease. One tumor was located suprabifurcal, seven tumors were located infrabifurcal, and in two cases there were subcardial bulky tumor masses. Tumor size ranged from 1 to 11 cm (mean 5.8 cm). Five tumors showed submucosal infiltration, three tumors showed an infiltration into the lamina muscularis propria, and two tumors extended into the adventitia/subserosa. Multifocality was observed in one case. According to the current TNM classification,[4] the five tumors with submucosal infiltration are classified into pT3 category, and the remaining cases into pT4a category.

Lymph node involvement was observed in three cases, and lymphatic vessel invasion could be detected in four cases. Further histopathological examination revealed presence of melanoma *in situ* in five cases. Melanin pigmentation could be detected in nine cases. Growth pattern was solid in five cases and epithelioid in two cases. Spindle cell, spindle–epithelioid and alveolar growth pattern was observed in one case each. A detailed overview of the clinicopathological parameters is given in Table 1. Macroscopic and histological examples of tumors are given in Figures 1 and 2.

Table 1 Clinicopathological features of 10 primary esophageal melanomas

Case	*Gender*	*Age*	*Localization*	*Size (cm)*	*Invasion*	*pT*	*pN*	*LVI*	*Growth pattern*	In situ	*Melanin*	*Survival*
1	M	55	Infrabifurcal	6	Musc. propria	pT4a	0/34	No	Spindle–epithel.	No	Present	21
2	M	69	Infrabifurcal	7.5	Adventitia	pT4a	NA	Yes	Alveolar	Yes	Present	2
3	M	70	Suprabifurcal	5	Submucosa	pT3	1/12	Yes	Solid	Yes	Present	17
4	F	69	Infrabifurcal	2.8	Submucosa	pT3	5/14	Yes	Epithelioid	No	Present	5
5	F	75	Subcardial	6	Musc. propria	pT4a	0/19	No	Solid	No	Present	4
6	M	57	Infrabifurcal	8	Submucosa	pT3	0/10	No	Solid	Yes	Absent	4
7	F	62	Infrabifurcal	1	Submucosa	pT3	0/20	No	Solid	No	Present	11
8	M	62	Infrabifurcal	2	Submucosa	pT3	0/40	No	Epithelioid	No	Present	24
9	M	68	Subcardial	11	Adventitia	pT4a	0/40	No	Solid	Yes	Present	35
10	M	56	Infrabifurcal	9	Musc. propria	pT4a	1/23	Yes	Spindle	Yes	Present	3*

pT = pT category according to UICC; pN = pN category according to UICC; LVI = lymphatic vessel invasion; *in situ* = presence of melanoma *in situ*. Survival is given in months.
*Patient still alive.

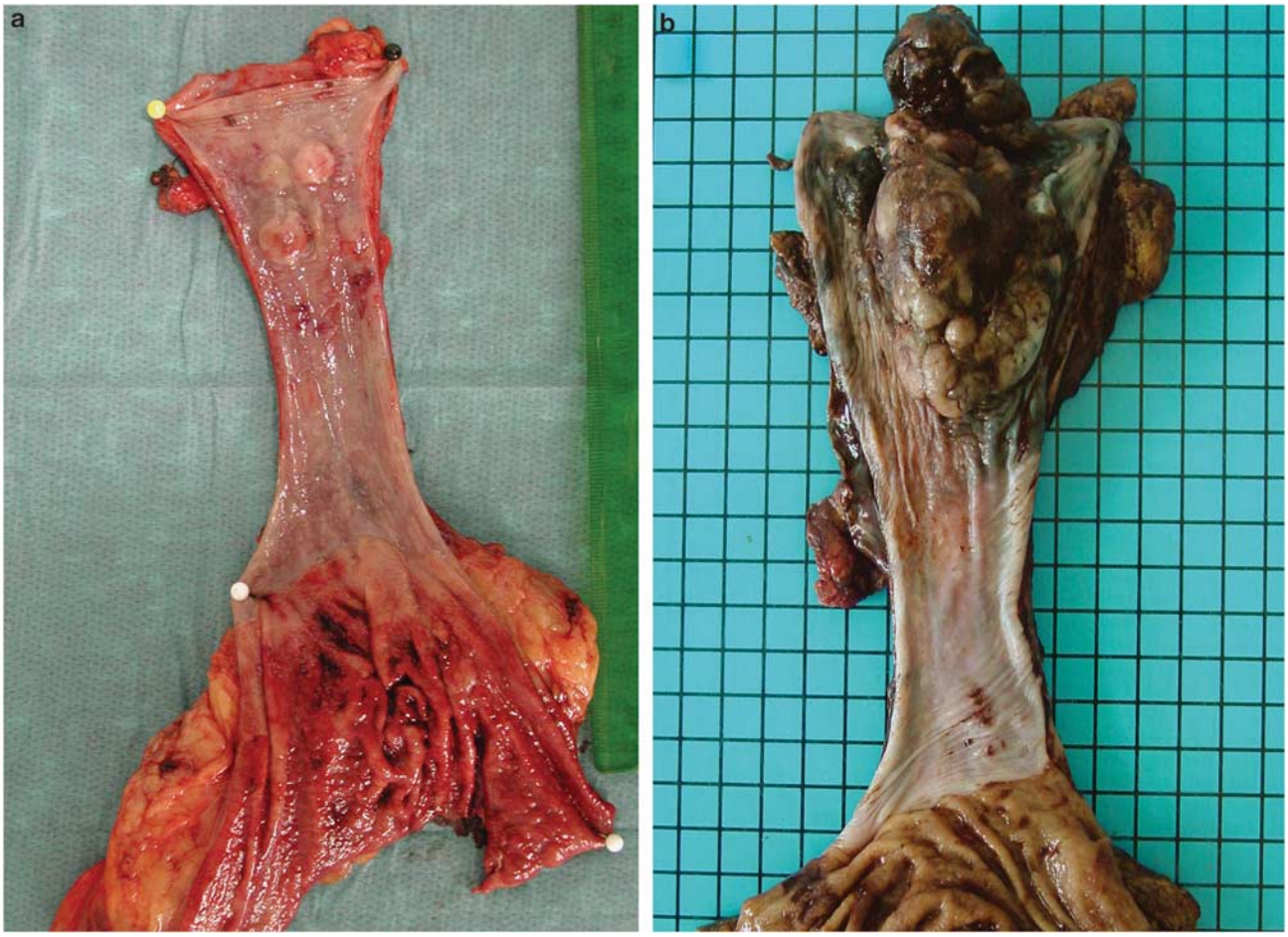

Figure 1 Macroscopical examples of primary esophageal melanomas. Esophagectomy specimen with examples of (**a**) a multifocal tumor (case 7) and (**b**) a large exophytic tumor mass (case 10).

Molecular Findings

In total, two *c-Kit* mutations, one *kRas* mutation and one *BRAF* mutation could be detected. In detail, one tumor (case 1) had a *c-Kit* missense mutation (c.1510T>C; p.F504L) and a *kRAS* mutation (c.34G>A; p.G12S). Case number 7 had a different *c-Kit* mutation (c.1507_1508 ins TTGCCT). Case number 8 had a V600E *BRAF* mutation. None of the cases had a *PDGFRA* mutation or a *NRAS* mutation (see Table 2).

Immunohistochemical Findings

c-Kit (CD117) expression could be detected in all cases. In all cases, in >50% of the tumor cells, c-KIT staining could be detected, but only in one case

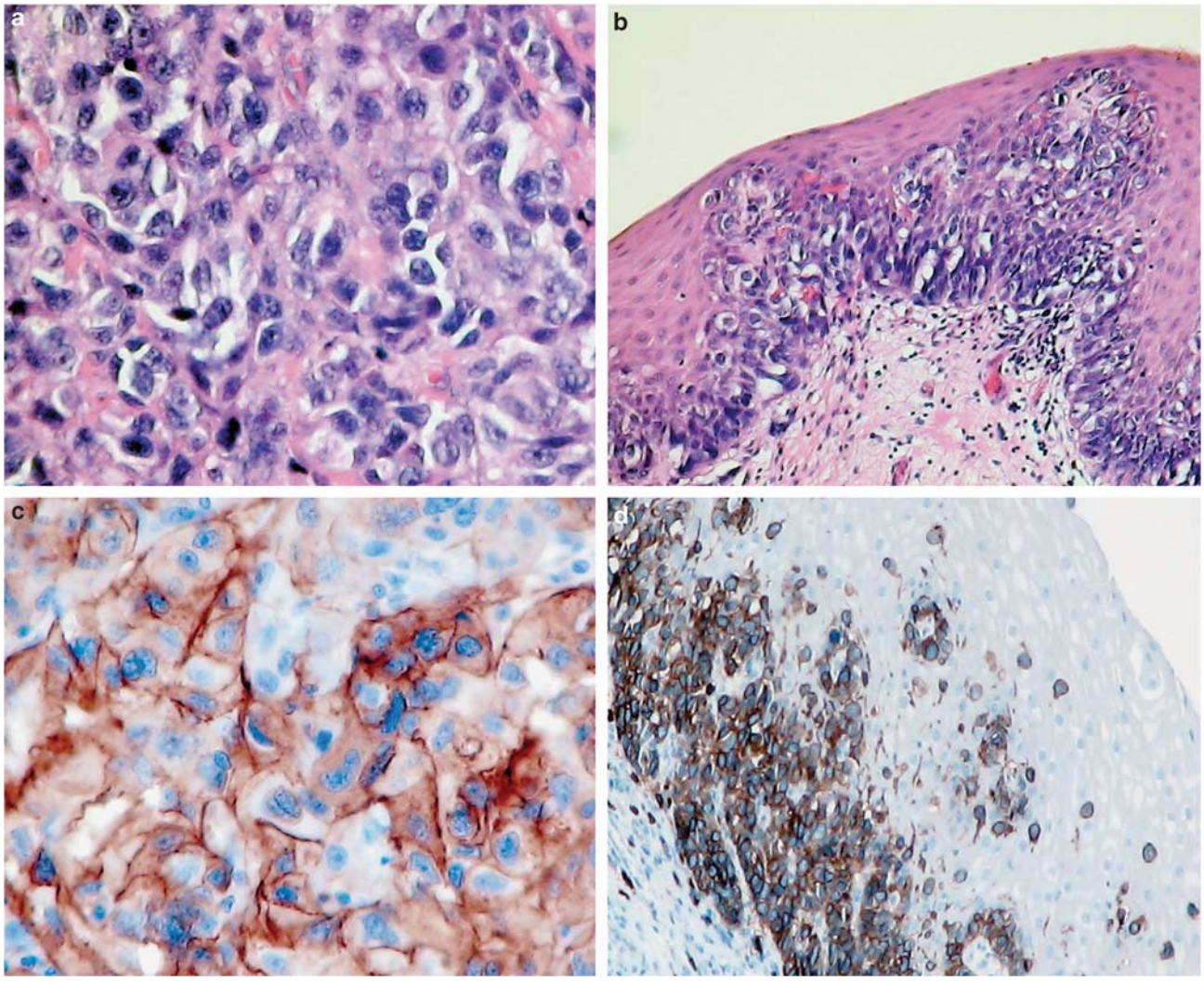

Figure 2 Photomicrographs of primary esophageal melanomas. (**a**) Histological picture of a spindle–epithelioid growth pattern (H&E stain, original magnification ×400). (**b**) Example of melanoma *in situ* (H&E stain, ×200), which is also highlighted by c-kit immunohistochemistry (**d**; original magnification ×200). (**c**) Another example of strong (+3) c-kit immunoreaction (original magnification ×400).

Table 2 Molecular and immunohistochemical (IHC) findings in 10 primary esophageal melanomas

Case	*C-KIT*	*PDGFR*	*K-RAS*	*N-RAS*	*B-RAF (V600E)*	*C-KIT IHC*	*PDGFR-A IHC*
1	c.1510T>C; p.Phe504Leu	WT	c.34G>A; p.Gly12Ser	WT	No	3+	Neg
2	WT	WT	WT	WT	No	2+	Neg
3	WT	WT	WT	WT	No	2+	Neg
4	WT	WT	WT	WT	No	1+	Neg
5	WT	WT	WT	WT	No	2+	Neg
6	WT	WT	WT	WT	No	3+	Neg
7	c.1507_1508 ins TTGCCT; p.A502_Y503insFA	WT	WT	WT	No	3+*	Neg
8	WT	WT	WT	WT	Yes	1+	Neg
9	WT	WT	WT	WT	No	2+	Neg
10	WT	WT	WT	WT	No	2+	Neg

WT=wild type.
*All cases showed c-kit immunohistochemical expression in >50% of the tumor cells; in case 7, >95% of the tumor cells were stained.

(case 7) there was a homogeneous strong staining in all tumor cells. The remaining cases showed a heterogeneous staining pattern. Three cases (cases 1, 6 and 7) showed high c-Kit expression (+3), among them the two cases with *c-Kit* mutations (cases 1 and 7). Five cases showed a moderate

expression (+2) and two cases demonstrated a weak expression (+1). None of the tumors showed immunohistochemical expression of PDGFRA (see Figure 1 and Table 2).

Correlation between Molecular and Immunohistochemical Findings and Clinicopathological Parameters

In this small series of tumors, none of the clinicopathological features, such as tumor size, pT category, depth of invasion, lymph node involvement or histopathological growth pattern, was significantly associated with prognosis. Only the presence of lymphatic vessel invasion was associated with a worse prognosis, although the difference was not statistically significant ($P=0.24$). Moreover, neither mutational status (*c-Kit*, *kRAS* or *BRAF* mutation absent *versus* present) nor immunohistochemical c-Kit expression was associated with patient prognosis (estimated using Kaplan–Meier curves and log rank tests).

Discussion

In cutaneous and noncutaneous melanomas, activation of the MAPK (RAS/RAF/MEK/ERK) pathway[6,9,10] and alterations of c-Kit[8,9,16] have an important role in oncogenesis and may offer potential targets for specific therapy.[6,7,17] There has been evidence that tumorigenesis in melanoma subtypes depends on the site of origins and on the presence of chronically sun-induced damage.[8,10,18] Therefore, oncogenic transformation of mucosal melanocytes in the esophagus may differ from those from other sites. As esophageal melanoma is an extremely rare entity, and literature holds only case reports or small case series, in particular molecular information about this disease is scarce. However, there is emerging need for therapeutic options in addition to surgical treatment, because of the highly aggressive behavior of this type of cancer. Here, we present a single-center study of rare primary esophageal melanoma with respect to clinicopathological and moleculargenetic features.

Comparable with other reports, the mean age of patients with esophageal melanoma was 65 years, and the male/female ratio of 7:3 showed a slight male predominance, which is concordant to data from literature. Clinical course was lethal in the majority of the cases (9/10) after a short period, with a median survival of 10 months after resection. This aggressive behavior, which can also be observed in mucosal melanomas of other anatomic sites, is reflected by the current TNM classification, where all mucosal melanomas of the upper aerodigestive tract are classified into a pT3 or pT4 category depending on the depth of a tumor invasion beyond the submucosa, whereas a pT1 or pT2 category does not exist. For esophageal melanomas, infrabifurcal localization is typical as in our series. Another constant finding in our study and in literature is the variety of growth patterns with solid, epithelioid or spindle cell morphology.[3,5] The frequent presence of melanoma *in situ* proved the esophageal mucosa being the primary site of the tumors, although metastatic disease could be ruled out by dermatological consultation and patient history in every case.

BRAF V600E mutations are most common in melanoma, with reports of up to 40% prevalence in cutaneous melanoma.[6,8,9] However, in mucosal melanoma, *BRAF* mutations occur at a lower frequency,[10] concordant to our findings with only one case harboring the hot spot V600E mutation. In contrast, *NRAS* mutations were found to exist in various frequencies in esophageal and other mucosal melanomas,[12,19] suggesting an additional activation mechanism in the MAPK pathway. We could not detect the presence of *NRAS* mutations in our series of esophageal melanomas, but we could demonstrate the presence of one *kRas* mutation (p.G12S), thereby confirming the impact of RAS alterations on oncogenesis of mucosal melanoma.

Molecular analysis for *c-Kit* revealed one tumor harboring a *c-Kit* missense mutation in exon 9 (c.1510T>C; p.Phe504Leu), which interestingly also showed a *KRAS* mutation. A different c-*Kit* mutation in exon 9 (c.1507_1508 ins TTGCCT; p.A502_Y503insFA) was detected in another case. These *c-Kit* mutations have not yet been described in the Sanger COSMIC (Catalogue of Somatic Mutations in Cancer) databank. The presence of *c-Kit* mutations may contribute to response to specific tyrosin kinase inhibitor therapy, and therefore molecular screening for *c-Kit* mutations may be helpful for identifying alternative therapeutic options in esophageal melanoma. The occurrence of *c-Kit* mutations in esophageal melanoma has been reported recently in the literature,[11,12] but the studies analyzed only exons 11, 13 and 17, but not exon 9, where we could detect two mutations and which encodes for the extracellular domain of the c-Kit protein.

For gastrointestinal stromal tumors, which frequently demonstrate *c-Kit* mutations, treatment with tyrosine kinase inhibitor sunitinib has been demonstrated to be particularly effective in tumors with exon 9 mutations. In addition, the mutational status of *c-Kit* has been shown to be important for the applied dosage when treated with imatinib.[20] Thus, our findings of the exon 9 mutations in esophageal melanoma may guide a particular treatment using tyrosine kinase inhibitors, and mutation analysis should also encompass this region for more accurate determination of the mutational status.

In one tumor with a *c-Kit* exon 9 mutation, we identified a mutation in the *KRAS* gene. Involvement of *NRAS* is well known in this tumor type; however, to the best of our knowledge mutation in *KRAS* has never been described in esophageal melanoma. Furthermore, the finding of the simultaneous

occurrence of two mutations, one in *c-Kit* and the other in the *KRAS*, is unusual. Concerning RAS isoforms, a different oncogenic potential has been reported for NRAS and KRAS in melanocytes, with a higher tumorigenic potency of NRAS. For mutant KRAS, the expression of a cooperating oncogene was necessary to reach a comparable transforming capacity, as mutant NRAS in a genetically well-defined system using NRAS and KRAS transformed melanocytes.[21] Thus, the simultaneous occurrence of *c-Kit* and a *KRAS* mutation may reflect such a cooperating oncogenic activity in a subset of esophageal melanomas. Interestingly, we could not confirm the results of a Japanese study, which showed a frequent occurrence of *NRAS* mutations in esophageal melanomas.[12] However, the patients of this study may harbor a different genetic background compared with our Caucasian collective.

Immunohistochemical c-Kit expression could be detected in all cases. Among the three cases showing high c-Kit expression, two cases harbored *c-Kit* mutations. However, immunohistochemistry has not been demonstrated to be a valid method for determination of therapeutic decisions with regard to TKI treatment in melanomas,[22] and staining results may be inconsistent and may be dependent on different staining protocols or fixations. This may also explain the discrepancies between our observations and the results of others, where immunohistochemical expression of c-Kit was reported to occur at a very low frequency.[12] However, a recent publication showed a significant correlation between immunohistochemical c-Kit staining and *c-KIT* mutation status in acral-lentiginous or mucosal-type melanomas.[15] In our study, both cases with *c-Kit* mutations had a high c-Kit immunohistochemical expression, which is consistent with the findings of this paper.

The phenomenon that one tumor had both *c-Kit* mutations and a mutation affecting the RAS pathway lacks explanation or comparable examples in literature but may reflect the complexity of molecular alterations in melanoma in general. Finally, it is noteworthy that none of the cases had a *PDGFRA* mutation, and also none of the tumors showed immunohistochemical expression of PDGFRA; thus, the role of PDGFR in esophageal melanoma may be disregarded.

In summary, we demonstrate that primary esophageal melanomas of Caucasian patients harbor mutations of *c-Kit*, *KRAS* and *BRAF* in varied frequencies. Molecular analysis may be helpful for the identification of targets for a specific therapy as an additional treatment option in selected patients with these highly malignant tumors.

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Disclosure/conflict of interest

The authors declare no conflict of interest.

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