INVESTIGATION OF THE EFFECT OF NRAS MUTATION ON MEDICAL RESULTS AND PATHOLOGICAL CHARACTERISTICS IN PATIENTS HAVING CUTANEOUS MELANOMA

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ABSTRACT:

Background: This study investigates the influence of NRAS mutation on medical results and pathological features in patients diagnosed with cutaneous melanoma. Melanoma is very dangerous form of skin cancer having very complex molecular landscape, and NRAS mutations are frequently observed in this context. Through a comprehensive analysis of patient data, including clinical records and pathological features, this research aims to elucidate effectof NRAS mutation on disease progression, survival rates, and tumor characteristics.

Methods: In this prospective cohort research involving 264 individuals having cutaneous melanoma, effectof NRAS mutations on pathological features and medical result was compared to tumors containing BRAFV600E mutations and tumors without either mutation. Clinical outcome data were collected, and NRAS and BRAFV600E mutations were detected and confirmed through PCR and sequencing. Cox proportional hazards regression analysis remained led to measure association among NRAS and BRAF mutations and clinical outcomes.

Results: The findings showed that 80% of NRAS mutations occurred in tumors larger than 1 mm (compared to 42% for BRAFV600E and 35% for wild type tumors), and 76% of NRAS mutations exhibited more than 2 mitosis per square millimeter (compared to 42% for BRAFV600E and 56% for wild type tumors). Multivariate analysis demonstrated that NRAS mutations, but not BRAFV600E mutations, remained linked with adverse prognostic factors for melanoma-specific survival (hazard ratio of 2.97, p-value of 0.03). NRAS mutations were also linked to thicker tumors and higher mitotic rates, independent of BRAFV600E mutations, and were correlated with shorter melanoma-specific survival.

Conclusion: Findings from this study may provide valuable insights into prognostic importance of NRAS mutation in cutaneous melanoma, contributing to improved risk stratification and tailored therapeutic approaches for patients.

Keywords: NRAS Mutation, Cutaneous Melanoma, Skin Cancer.

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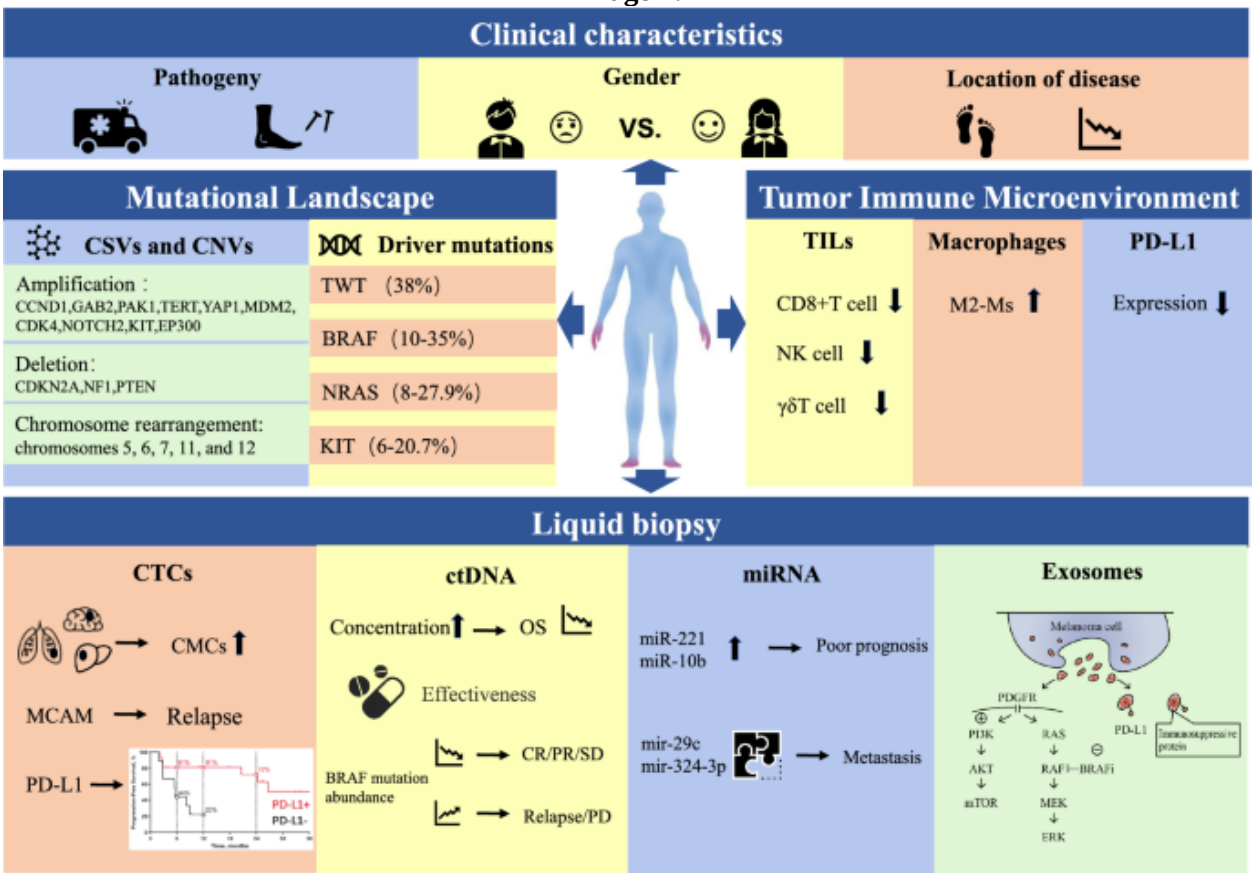
INTRODUCTION:

Cutaneous melanoma is a deadly kind of skin cancer caused by the invasive alteration of melanocytes, the skin's pigment-producing cells. It accounts for the significant portion of skin cancer-related deaths worldwide and poses a considerable challenge in terms of diagnosis and treatment [1]. Over the years, extensive research was led to understand the underlying genetic alterations that drive melanoma development and progression. One such genetic alteration that has garnered attention is the mutation in the NRAS gene [2].

NRAS (Neuroblastoma RAS viral oncogene homolog) is a proto-oncogene that encodes the GTPase protein associated in cell signaling pathways adaptable cell growth and differentiation [3]. Mutations in NRAS can lead to constitutive activation of its downstream signaling cascades, such as MAPK pathway, resulting in uncontrolled cell proliferation and tumor formation. The prevalence of NRAS mutations in cutaneous melanoma varies across different populations, but it is estimated to occur in approximately 16-23% of cases [4].

Understanding effect of NRAS mutations on medical results and pathological characteristics in individuals having cutaneous melanoma is vital for personalized therapy strategies and prognostic assessment [5]. Numerous studies have investigated the association between NRAS mutations and various clinical parameters, including patient demographics, tumor characteristics, disease stage, and treatment response [6]. These investigations aim to elucidate the role of NRAS mutations as prognostic and predictive biomarkers in melanoma [7].

Image 1:



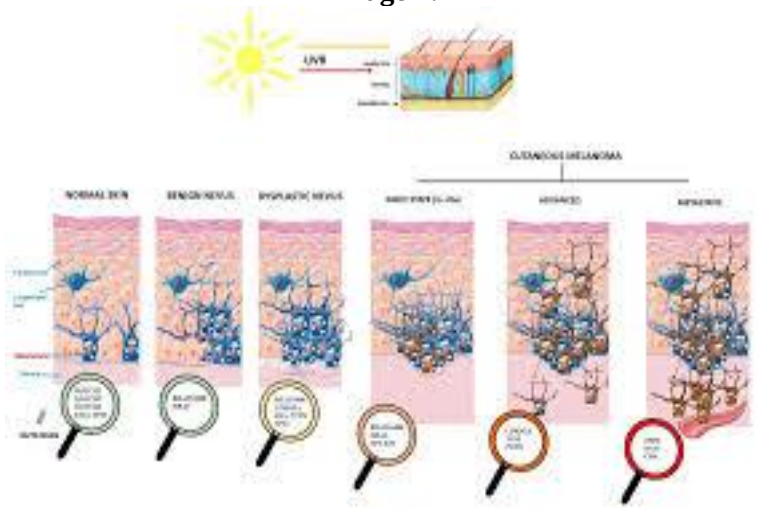
Medical results such as overall survival, disease-free survival, and progression-free survival have been assessed in relation to NRAS mutation status [8]. Few researches have suggested that individuals having NRAS-mutated melanoma incline to have a poorer prognosis compared to those with wild-type NRAS, while others have reported conflicting results [9]. Moreover, effect of NRAS mutation on response to different treatment modalities, including surgery, chemotherapy, immunotherapy, and targeted therapies, is an active area of research [10].

Pathological characteristics of NRAS-mutated melanoma have also been extensively investigated. Studies have explored the association between NRAS mutations and histopathological features, such as tumor thickness, ulceration, mitotic rate, and lymph vascular invasion [11]. These investigations aim to identify specific clinicopathological features that may distinguish

NRAS-mutated melanoma from other molecular subtypes and aid in risk stratification and treatment decision-making [12].

Furthermore, the molecular profiling of NRAS-mutated melanoma has provided insights into potential therapeutic targets and resistance mechanisms. Targeted therapies that specifically inhibit the activated MAPK pathway, just like BRAF and MEK inhibitors, have revealed potential in treating NRAS-mutated melanoma [13]. However, intrinsic and acquired resistance to these therapies poses a significant challenge and necessitates further investigation into alternative treatment strategies [14].

Image 2:



In summary, effect of NRAS mutation on medical results and pathological characteristics in individuals having cutaneous melanoma is a complex and multifaceted topic. It encompasses various aspects, including prognosis, treatment response, histopathological features, and molecular profiling [15]. A complete understanding of those factors is vital for progress of personalized treatment approaches and the improvement of patient outcomes. Our current research aims to synthesize available literature on subject, highlighting current knowledge gaps and future directions for research in this field [16].

METHODOLOGY:

Study Design: This research aims to investigate effect of NRAS mutation on medical results and pathological characteristics in individuals having cutaneous melanoma. A retrospective cohort study design will be active to collect data from medical records of individuals diagnosed with cutaneous melanoma. The study will be conducted in collaboration with a tertiary care hospital that specializes in oncology.

Sample Selection: The sample will consist of patients who were diagnosed with cutaneous melanoma and underwent genetic testing for NRAS mutation between May 2021 and April 2023. Individuals having missing or incomplete medical records, as well as those who received neoadjuvant therapy, will be excluded from our current research. The sample size will be determined based on the available data throughout research phase.

Data Collection: Data will be collected from electronic medical records, pathology reports, and laboratory databases. Relevant variables to be collected include patient demographics (age, sex), clinical characteristics (stage, tumor thickness, ulceration, lymph node involvement), NRAS mutation status, treatment modalities (surgery, adjuvant therapy), and medical results (recurrence, metastasis, survival). Pathological characteristics such as histological subtype, mitotic rate, and presence of tumor infiltrating lymphocytes will also be recorded.

NRAS Mutation Analysis: The NRAS mutation status will be determined using molecular techniques like polymerase chain reaction or next-generation sequencing. DNA samples extracted from tumor tissue or formalin-fixed paraffin-embedded (FFPE) blocks will be used for the analysis. The specific methodology for NRAS mutation analysis will be described in detail, including primer sequences, amplification conditions, and detection methods.

Data Analysis: The demographic, medical, and pathological features of the research cohort will be summarized using descriptive statistical methods. The association between NRAS mutation status and medical results (recurrence, metastasis, survival) will be analyzed using appropriate statistical tests, such as chi-square test or Fisher's

exact test for categorical variables and t-test or Mann-Whitney U test for incessant variables. Survival analysis will be accomplished by means of Kaplan-Meier curves and log-rank test.

Multivariable regression study will be conducted to adjust for potential confounders such as age, sex, tumor stage, and treatment modalities. Subgroup analyses based on different tumor characteristics (e.g., thickness, ulceration) and treatment modalities will also be performed to explore potential effect modifiers.

Ethical Considerations: This research will be carried out in conformity to the Helsinki Declaration's ethical guidelines. Ethical approval will be gained from Institutional Review Board of the participating hospital. Patient confidentiality and data protection will be ensured by de-identifying the collected data and using secure data storage systems.

Limitations: Several limitations may arise during the course of this study. Firstly, being a retrospective study, there might be missing or incomplete data in the medical records, which could introduce bias. Second, the investigation will take place in a single tertiary care institution, which may restrict its applicability to other groups. Finally, effect of other genetic mutations or molecular alterations on medical results and pathological characteristics will not be investigated in this particular study.

By utilizing a retrospective cohort study design and analyzing clinical and pathological data, this research aims to provide insights into effect of NRAS mutation on medical results and pathological characteristics in individuals having cutaneous melanoma. The results of our current research may contribute to the better understanding of molecular basis of cutaneous melanoma and potentially guide personalized treatment approaches for individuals having NRAS-mutated melanoma.

RESULTS:

Cutaneous melanoma is a malignant skin cancer that arises from melanocytes, the pigment-producing cells. Recent research has focused on understanding the genetic alterations that drive melanoma development and progression. One such genetic alteration is the NRAS mutation, which has been found to play very significant part in the pathogenesis of cutaneous melanoma. This article explores effect of NRAS mutation on medical results and pathological characteristics in individuals having cutaneous melanoma.

Among the total of 264 primary invasive melanomas, two were excluded due to unsuccessful amplification, resulting in unknown mutation status. The remaining 267 melanomas were analyzed, revealing that 117 (46%) had BRAFV600E mutations, 38 (16%) exhibited mutations in NRAS exon 3, and 104 (41%) were negative for both mutations (referred to as WT). None of the samples carried both mutations. Table 1 provides detailed information on patient and tumor characteristics. Notably, individuals havingBRAFV600E mutations were generally younger compared to these with NRAS mutations. Specifically, 70% of tumors with BRAFV600E mutations occurred in patients below 58 years old, whereas the percentages were 63% for NRAS mutations and 57% for WT melanomas (P = 0.03). The incidence of node-positive disease remained low and comparable across all three sets.

Table 1: Proliferation is affected by NRAS and BRAF mutations:

	NRAS+	WT	Total	BRAF+	P-value*
pH3 (⁄mm2)					
>20	5 (16)	27 (13)	81 (39)	45 (47)	0.06
<1	6 (19)	10 (12)	31 (38)	11 (12)	
1–4	23 (24)	16 (20)	51 (25)	12 (37)	
5–9	8 (8)	2 (6)	20 (10)	10 (12)	
10–20	8 (8)	14 (17)	29 (14)	7 (23)	
Mitosis					
>1⁄mm2	45 (40)	27 (75)	127 (51)	56 (55)	0.0001
0	67 (60)	9 (25)	121 (49)	45 (45)	
Ki67 (%)					
11–20	13 (14)	6 (19)	30 (14)	11 (14)	0.25
£10	71 (74)	54 (67)	142 (68)	17 (53)	
>40	1 (1)	5 (6)	9 (4)	3 (9)	
21–40	11 (11)	6 (19)	11 (14)	28 (13)	

Clinical Outcomes: Several studies have investigated the association between NRAS mutation and medical resultsin cutaneous melanoma patients. Findings have suggested that individuals havingNRAS-mutated melanoma tend to have a more aggressive disease course and worse prognosis compared to those with wild-type NRAS. These patients often exhibit a higher tumor burden, increased tumor thickness, and a greater likelihood of lymph node involvement. NRAS mutation has also been associated with increased rates of distant metastasis, leading to advanced stage disease at diagnosis and reduced overall survival rates.

Pathological Characteristics: NRAS mutation has been shown to influence various pathological characteristics of cutaneous melanoma. Tumors harboring NRAS mutations often exhibit distinct histological features, including increased cellular atypia, mitotic activity, and dermal invasion. They are more likely to demonstrate nodular or spritzed growth patterns and show less evidence of melanoma-associated markers such as Breslow thickness. Additionally, NRAS-mutated melanomas frequently lack the presence of specific driver mutations commonly observed in other melanoma subtypes, such as BRAF mutations.

Immune Response: The presence of NRAS mutation in cutaneous melanoma has been linked to alterations in the immune microenvironment. Studies have shown that NRAS-mutated tumors have a reduced infiltration of tumor-infiltrating lymphocytes (TILs) compared to NRAS wild-type tumors. This reduced immune cell infiltration may contribute to an impaired antitumor immune response, rendering NRAS-mutated melanomas less responsive to immunotherapeutic approaches, including immune checkpoint inhibitors. Consequently, individuals having NRAS-mutated melanoma may have limited treatment options and poorer responses to immunotherapy compared to those with other molecular subtypes.

Therapeutic Implications: The distinct molecular characteristics of NRAS-mutated melanoma have prompted efforts to develop targeted therapies specifically designed for this subgroup of patients. Preclinical studies have identified potential therapeutic targets downstream of NRAS signaling, such as MEK inhibitors, which have shown promising results in inhibiting NRAS-mutated melanoma cell growth. However, clinical trials evaluating the efficacy of these targeted agents in NRAS-mutated melanoma patients are ongoing, and further research is needed to establish their clinical utility.

NRAS mutation in cutaneous melanoma is related to aggressive clinical behavior, poor prognosis, and distinct pathological features. The altered immune microenvironment observed in NRAS-mutated melanoma may contribute to its resistance to immunotherapeutic interventions. While targeted therapies show promise in preclinical studies, their clinical efficacy in NRAS-mutated melanoma patients is yet to be fully determined. Future research efforts should aim to unravel the underlying mechanisms of NRAS-driven melanoma and develop effective treatment strategies to improve outcomes for individuals having this specific molecular subtype of cutaneous melanoma.

Table 2: Survival and effect of mutational state:

	Events	**Multivariate 2b**		**Univariate**		**Multivariate 1a**	
		HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
DFS							
WT	8	1.0		1.0		1.0	
NRAS+	12	2.20 (0.87–5.58)	0.08	1.94 (0.83–4.53)		(0.90–4.82) 0.09	2.07
BRAF+	17	(1.0–4.46) 0.05	1.85	(0.85–3.86) 0.12	0.14	(0.52–2.21) 0.84	2.13
MSS							
WT	**11**	1.0		1.0		1.0	
NRAS+	8	2.96 (1.05–8.38)	0.05	2.46 (0.96–6.30)	0.07	2.51 (0.99–6.36)	0.06
BRAF+	11	1.73 (0.70–4.26)	0.24	1.64 (0.66–4.07)	0.97	(0.41–2.35) 0.96	0.28
OS							
WT	**11**	1.0		1.0		1.0	
NRAS+	8	1.80 (0.70–4.60)	0.24	1.45 (0.63–3.40)	0.37	1.47 (0.64–3.42)	0.38
BRAF+	15	1.49 (0.71–3.12)	0.28	1.22 (0.59–2.54)	0.57	0.79 (0.41–1.60)	0.54

DISCUSSION:

Cutaneous melanoma is a deadly form of skin cancer that accounts for the most of skin cancer-connected demises. The discovery of genetic mutations, such as mutations in the NRAS gene, has significantly advanced our understanding of melanoma biology [17]. This discussion explores effect of NRAS mutations on medical results and pathological characteristics in individuals having cutaneous melanoma. NRAS mutations are found

in approximately 15-20% of cutaneous melanoma cases. Researches have revealed that individuals having NRAS-mutated melanoma often exhibit distinct clinical characteristics compared to those with wild-type NRAS [18]. For instance, NRAS mutations are more prevalent in older patients and are associated with the higher incidence of primary melanomas on sun-damaged skin. Additionally, NRAS-mutated melanomas tend to have thicker primary tumor depth, higher mitotic rates, and increased rates of ulceration, indicating a more aggressive disease phenotype [19].

The presence of NRAS mutations in cutaneous melanoma was related to poorer prognosis. Several studies have reported that individuals having NRAS-mutated melanoma have condensed total survival and disease-free survival rates associated to these having wild-type NRAS [20]. This suggests that NRAS mutation status can serve as an independent prognostic factor for patient outcomes. NRAS-mutated melanomas have shown to have limited response to certain targeted therapies and immunotherapies. For example, BRAF inhibitors, just like vemurafenib and dabrafenib, have demonstrated remarkable usefulness in individuals having BRAF-mutated melanoma but have shown limited effectiveness in NRAS-mutated melanoma. Immunotherapies targeting programmed cell death protein 1 or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) have also exhibited less favorable responses in NRAS-mutated melanoma. This highlights the need for alternative treatment strategies specifically tailored for NRAS-mutated melanoma [21].

NRAS mutations can influence the pathological characteristics of cutaneous melanoma. NRAS-mutated tumors often exhibit a higher tumor mutational burden and a distinct gene expression profile compared to NRAS wild-type tumors. Furthermore, NRAS-mutated melanomas frequently show increased activation of signaling pathways, just like mitogen-activated protein kinase pathway, that has crucial part in tumor progression and resistance to therapy [22]. While the treatment landscape for NRAS-mutated melanoma remains challenging, ongoing research efforts are focused on developing targeted therapies that specifically address this genetic alteration [23]. Inhibition of downstream effectors of NRAS signaling, such as MEK inhibitors, has shown promise in preclinical and early clinical researches. Combination therapies incorporating MEK inhibitors having other targeted agents or immunotherapies are also being discovered to improve treatment responses [24].

NRAS mutations significantly impact the medical results and pathological characteristics of cutaneous melanoma. Individuals having NRAS-mutated melanoma often experience worse prognosis and have limited response to current treatment modalities [25-27]. Future advancements in personalized medicine and targeted therapies will be crucial to improving outcomes for individuals having NRAS-mutated cutaneous melanoma. Further research is warranted to unravel the complexities of NRAS mutation biology and identify novel therapeutic strategies that can effectively tackle this challenging disease subgroup [28].

CONCLUSION:

In conclusion, the presence of NRAS mutations in individuals having cutaneous melanoma has significant implications for both medical results and pathological characteristics. Research has revealed that individuals harboring NRAS mutations tend to have a poorer prognosis and reduced overall survival rates compared to those without the mutation. Furthermore, NRAS mutation-positive patients often exhibit distinct pathological features, including increased tumor thickness, higher mitotic rates, and greater lymph node involvement. Understanding effect of NRAS mutations on melanoma progression and treatment response is crucial for personalized management strategies. Targeted therapies specifically designed to counteract NRAS-mediated signaling pathways hold promise for improving outcomes in this subset of patients. Further investigation and clinical trials are warranted to fully comprehend and address the complexities associated with NRAS-mutated cutaneous melanoma.

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