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Molecular-Genetic Profile of Nephroblastoma in Children in Uzbekistan: Clinical-Morphological Correlations and the Prognostic Significance of K-RAS Mutations.

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SUMMARY

Relevance. Nephroblastoma remains one of the leading malignant tumors of childhood. In a subset of patients, despite standard SIOP/COG protocols, early relapses and metastases occur, which are associated with unfavorable molecular profiles, including activation of the RAS/MAPK cascade and K-RAS mutations. Data on the pediatric population of Uzbekistan have previously been unavailable.

Objective of the study. To assess the frequency of K-ras gene mutations in children with nephroblastoma in Uzbekistan and to determine their association with tumor stage, organ invasion, metastasis, and treatment characteristics

Materials and methods. A retrospective analysis was conducted on 230 patients under 15 years of age with histologically confirmed nephroblastoma who were treated at the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology and its branches. Clinical and morphological parameters, Enneking stage, surgical volume, therapy regimens, recurrences, and regional and distant metastases were evaluated. K-ras mutations (codons 12 and 13) were identified using Sanger sequencing and/or NGS. Statistical analysis included χ^2 testing, with $p < 0.05$ considered significant.

Results. K-ras mutations were detected in 23 (10.0%) of the 230 patients. Their frequency increased with age and tumor stage, reaching 76.5% in stage IV. Mutations were significantly more common in cases of relapse (33.3% vs. 2.3%), in the presence of regional (15.7% vs. 6.6%) and distant metastases (36.4% vs. 3.8%), as well as in patients who received only chemotherapy and palliative interventions.

Conclusion. K-ras mutation is a rare but highly informative marker of aggressive nephroblastoma, associated with advanced stages, organ invasion, relapse, and metastasis. Incorporating K-ras analysis into the risk stratification system for children with nephroblastoma in Uzbekistan may improve individualized treatment and the accuracy of prognostic assessment.

KEYWORDS: Nephroblastoma, Wilms Tumor, K-Ras, Children, Organ Invasion, Metastasis, Relapse, Uzbekistan..

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INTRODUCTION

Nephroblastoma (Wilms tumor) remains one of the key challenges in modern pediatric oncology, being the most common malignant kidney tumor in children and accounting for up to 6–7% of all solid childhood neoplasms. Despite significant advances in combined therapy achieved through the SIOP and COG protocols, the biological behavior of the tumor remains unpredictable in some cases, and the risk of early relapse and distant metastases remains high in patients with aggressive molecular profiles [2]. Current concepts of nephroblastoma pathogenesis emphasize the role of molecular oncology, particularly genetic and epigenetic alterations that regulate proliferation, differentiation, and the invasive potential of tumor cells. Over the past decade, research attention has increasingly focused on signaling pathways involved in the embryonic development of renal tissue. Among these, the RAS/MAPK cascade is of particular importance, as it regulates the cell cycle, growth, migration, and apoptosis. Dysregulation of this pathway is associated with the development of an aggressive tumor phenotype, chemotherapy resistance, and a high risk of metastatic spread [3, 7].

One of the key genes involved in the activation of RAS/MAPK signaling is **K-ras**, which encodes a small GTP-binding protein that plays a critical role in the transduction of mitogenic signals. In nephroblastoma cells, K-ras mutations lead to constitutive activation of the proliferative cascade, increased mitotic activity, enhanced invasive potential, and early hematogenous metastasis, as repeatedly demonstrated by Williams et al. (2010), Perotti et al. (2016), and Wegert et al. (2018) [5, 9, 10]. Although the frequency of K-ras mutations in nephroblastoma is relatively low compared to other pediatric tumors, their presence correlates with an extremely unfavorable disease course, including anaplastic forms, large tumors, vascular invasion, and early relapses [8]. Despite international progress in understanding the molecular biology of nephroblastoma, regional characteristics remain insufficiently studied. It has been shown that the molecular profile of the tumor may vary between populations due to differences

in genetic background, environmental factors, access to early diagnosis, and applied therapeutic protocols [1]. In particular, in countries with developing oncology systems, tumors are more often diagnosed at advanced stages, with large primary masses and pronounced invasive features, which may reflect a different pattern of molecular alterations compared to cohorts in the USA or Europe.

For Uzbekistan, where nephroblastoma is one of the leading solid tumors in children, systematic data on the molecular-genetic profile, including K-ras mutations, have been virtually nonexistent. To date, no study has conducted a comprehensive assessment of the prevalence of K-ras mutations, their association with morphological characteristics, disease stage, metastatic potential, and prognosis. The absence of such data complicates the development of national risk-stratification protocols and limits the ability to individualize therapy.

In this context, the study of K-ras mutations in a cohort of children in Uzbekistan acquires significant clinical and scientific importance. Determining the role of this marker will allow:

1. Identification of high-risk groups with an unfavorable disease course;
2. Optimization of surgical and pharmacological treatment strategies;
3. Development of personalized monitoring protocols;
4. Integration of molecular diagnostics into the national patient management model.

Thus, the study of K-ras mutations and their clinicopathological and prognostic correlations represents a relevant research direction with a direct impact on improving treatment outcomes for children with nephroblastoma in Uzbekistan, bringing domestic pediatric oncology closer to international standards of molecular stratification.

STUDY OBJECTIVE

The aim of this study was to assess the frequency of K-ras gene mutations in children with nephroblastoma in Uzbekistan and to determine their association with the tumor's clinicopathological characteristics, organ invasion, metastatic spread, and treatment strategies. Additionally, the results were compared with international data to clarify the prognostic role of K-ras in risk stratification and in selecting therapy intensity.

MATERIALS AND METHODS

This retrospective analytical study included 230 patients with histologically confirmed nephroblastoma who were under observation and treatment at the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology (RSSPMCOR) and its branches. Patients up to 15 years of age with complete clinical and diagnostic documentation who had undergone standard treatment protocols were included. Patients without morphological verification, with other malignant neoplasms, or with incomplete data were excluded.

Morphological evaluation was performed on standard hematoxylin-eosin–stained sections, assessing the degree of differentiation (G1–G4), tumor architecture, and signs of anaplasia. Staging was carried out using the Enneking system, which allows for an objective assessment of local tumor spread and the presence of regional or distant metastases.

Instrumental diagnostics included ultrasonography, multi-slice computed tomography (CT), and magnetic resonance imaging (MRI). Tumor maximum dimensions, invasion of organs and vessels (liver, intestines, inferior vena cava, paravertebral muscles), as well as signs of local and systemic dissemination, were assessed.

Molecular-genetic analysis was performed on tumor tissue obtained during surgery. DNA was extracted using standard methods, followed by amplification and sequencing of K-ras gene regions, primarily codons 12 and 13 of exon 2. Direct Sanger sequencing or high-throughput next-generation sequencing (NGS) was employed, providing high sensitivity for mutation detection.

For the analysis of clinicopathological and prognostic characteristics, patient age, sex, disease stage, tumor differentiation, extent of surgical intervention, treatment regimen, presence of relapse, regional and distant metastases, and their timing were evaluated. Statistical analysis included descriptive statistics and the χ^2 test for group comparisons. A p-value < 0.05 was considered statistically significant.

STUDY RESULTS

In the studied cohort of 230 children with nephroblastoma, K-ras mutations were detected in 23 cases (10.0%), consistent with international literature reporting their relatively rare but clinically significant occurrence.

Age-stratified analysis showed a pronounced tendency for increased mutational activity in older patients: among children under 3 years, mutations were detected in 7.4%, whereas in the group over 3 years, the frequency increased to 13.7%, suggesting a possible relationship between age and the molecular evolution of the tumor.

Gender-based comparison revealed that mutations were slightly more common in boys (12.0%) than in girls (7.2%), indicating a potential influence of sex-related factors on the molecular-genetic characteristics of the tumor.

The most significant differences were observed in the analysis of disease stages according to the Enneking system. At early stages (1A and 1B), no mutations were detected, indicating their absence in localized, favorable tumor forms. In stage II, the mutation

frequency was 9.1%, increasing to 14.6% in stage III, and reaching a maximum of 76.5% in stage IV, reflecting a direct association of K-ras mutations with aggressive disease course, extensive tumor spread, and metastatic potential.

Table 1.
Distribution of K-ras mutations in children with nephroblastoma by age, sex, and disease stage

Parameter	Not tested	Mutation detected	No mutation	No data	Total
Age					
Up to 3 years	64 (47,4%)	10 (7,4%)	59 (43,7%)	2 (1,5%)	135 (58,7%)
Over 3 years	55 (57,9%)	13 (13,7%)	24 (25,3%)	3 (3,2%)	95 (41,3%)
Sex					
Girls	44 (45,4%)	7 (7,2%)	45 (46,4%)	1 (1,0%)	97 (42,2%)
Boys	75 (56,4%)	16 (12,0%)	38 (28,6%)	4 (3,0%)	133 (57,8%)
Disease Stage					
1B – G1–2, T2a,bM0	48 (52,2%)	0 (0,0%)	44 (47,8%)	0 (0,0%)	92 (40,0%)
1A – G1–2, T1a,bM0	5 (55,6%)	0 (0,0%)	4 (44,4%)	0 (0,0%)	9 (3,9%)
2A – G3–4, T1a,bM0	9 (81,8%)	1 (9,1%)	1 (9,1%)	0 (0,0%)	11 (4,8%)
2B – G3–4, T2aM0	25 (75,8%)	0 (0,0%)	4 (12,1%)	4 (12,1%)	33 (14,3%)
3A – G3–4, T2bM0	3 (15,0%)	2 (10,0%)	15 (75,0%)	0 (0,0%)	20 (8,7%)
3B – G1–4, T1–2N1	27 (56,2%)	7 (14,6%)	13 (27,1%)	1 (2,1%)	48 (20,9%)
IV – G1–4, T1–2M1	2 (11,8%)	13 (76,5%)	2 (11,8%)	0 (0,0%)	17 (7,4%)
Total	119 (51,7%)	23 (10,0%)	83 (36,1%)	5 (2,2%)	230 (100,0%)

Analysis of data from 230 patients with nephroblastoma showed a pronounced association of K-ras mutations with organ invasion and tumor spread.

According to ultrasonography, among patients without signs of tumor dissemination, the mutation frequency was 9.4%, indicating relatively low mutational activity at early stages of localized growth. In cases of invasion into the paravertebral muscles and soft tissues, the mutation frequency was comparable at 9.8%, reflecting a moderate increase in aggressiveness with local tumor spread. However, in cases of liver invasion, the mutation frequency reached a maximum of 66.7%, confirming the role of K-ras as a marker of aggressive tumor biology. Involvement of major vessels, particularly the inferior vena cava, was associated with mutations in 9.1% of cases. No mutations were detected in cases with spleen or colon involvement, likely due to the very small number of observations.

According to multi-slice CT (MSCT) data, a similar trend was observed. K-ras mutations were not detected in cases of gastric invasion; however, when the tumor involved the intestines, the mutation frequency reached 55.6%, and in cases of liver involvement, it again reached 66.7%, consistent with the ultrasonography findings. Invasion of the inferior vena cava was associated with mutations in 17.6% of cases, exceeding the ultrasound-based values and reflecting the more precise visualization of vascular involvement provided by MSCT. Among patients without signs of tumor dissemination on MSCT, mutations were detected in only 4.5%, highlighting their predominant association with invasive tumor phenotypes.

According to MRI, which provides the highest accuracy in assessing vascular and perinephric invasion, the most pronounced differences were observed. In cases of invasion of the inferior vena cava, K-ras mutations were detected in all observations (100%), indicating a strong association between this molecular alteration and severe vascular invasion. In the absence of tumor spread, the mutation frequency was 6.2%, confirming its rarity in localized forms. For liver and gastric invasion, no mutations were detected on MRI, likely due to the very small number of observations and insufficient statistical power. Interestingly, in the group with insufficient MRI data, mutations were recorded in 11.3%, which may reflect either a sampling bias or a clinically more severe cohort that was more frequently referred for additional imaging studies.

Table 2.
Distribution of K-ras mutations according to organ invasion and tumor spread based on ultrasonography, multi-slice CT, and MRI data (n = 230)*

Site of Invasion / Tumor Spread	Not assessed	Mutation detected	No mutation	No data	Total
Ultrasonography data					
None (no spread)	77 (48,4%)	15 (9,4%)	63 (39,6%)	4 (2,5%)	159 (69,1%)
Paravertebral muscles / Soft tissues	39 (76,5%)	5 (9,8%)	7 (13,7%)	0 (0,0%)	51 (22,2%)
Liver	0 (0,0%)	2 (66,7%)	1 (33,3%)	0 (0,0%)	3 (1,3%)
Major vessels (inferior vena cava, etc.)	0 (0,0%)	1 (9,1%)	9 (81,8%)	1 (9,1%)	11 (4,8%)
Spleen	2 (40,0%)	0 (0,0%)	3 (60,0%)	0 (0,0%)	5 (2,2%)
Colon	1 (100,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	1 (0,4%)
MSCT data					
Stomach	2 (40,0%)	0 (0,0%)	3 (60,0%)	0 (0,0%)	5 (2,2%)
Small / large intestine	4 (44,4%)	5 (55,6%)	0 (0,0%)	0 (0,0%)	9 (3,9%)
Inferior vena cava	12 (70,6%)	3 (17,6%)	2 (11,8%)	0 (0,0%)	17 (7,4%)

Liver	0 (0,0%)	2 (66,7%)	1 (33,3%)	0 (0,0%)	3 (1,3%)
No spread	76 (49,4%)	7 (4,5%)	66 (42,9%)	5 (3,2%)	154 (67,0%)
No data	25 (59,5%)	6 (14,3%)	11 (26,2%)	0 (0,0%)	42 (18,3%)
MRI data					
Stomach	2 (33,3%)	0 (0,0%)	4 (66,7%)	0 (0,0%)	6 (2,6%)
Inferior vena cava	0 (0,0%)	2 (100,0%)	0 (0,0%)	0 (0,0%)	2 (0,9%)
Liver	1 (100,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	1 (0,4%)
No spread	36 (45,0%)	5 (6,2%)	39 (48,8%)	0 (0,0%)	80 (34,8%)
No data	80 (56,7%)	16 (11,3%)	40 (28,4%)	5 (3,5%)	141 (61,3%)
Total	119 (51,7%)	23 (10,0%)	83 (36,1%)	5 (2,2%)	230 (100,0%)

The data indicate a clear association between K-ras mutations and treatment strategies, reflecting the direct influence of the tumor's molecular characteristics on clinical decision-making.

Analysis by treatment approach showed the lowest mutation frequency in patients receiving combined therapy (6.4%) and comprehensive treatment (12.3%), consistent with the relatively controlled disease course in these groups. The highest mutation frequency was observed in patients who received chemotherapy alone—37.5%—likely because this category more often included clinically severe and unresectable cases. The mutation frequency in the "surgery only" group was 9.4%, correlating with predominantly localized tumor forms.

Particularly significant differences were observed when assessing the extent of surgical intervention. In cases of radical nephroureterectomy with mandatory lymphadenectomy, the mutation frequency was only 3.9%, whereas the absence of lymphadenectomy increased this rate to 32.7%. This reflects the fact that patients with biologically aggressive, mutation-positive tumors more often underwent limited interventions due to advanced stage, metastatic, or invasive phenotypes, rather than the reverse. In the single case where no surgery was performed, no mutations were detected.

Equally informative is the analysis of surgical treatment goals. The mutation frequency in palliative interventions reached 80%, clearly indicating an association of K-ras with an extremely unfavorable clinical phenotype—large, unresectable, metastatic tumors. In the radical surgery group, mutations were detected in only 6.9% of patients, and they were completely absent in the subgroup undergoing semi-radical procedures.

Analysis of combined therapy regimens demonstrates that more intensive protocols, including repeated chemotherapy (CT → surgery → CT), were associated with a mutation frequency of 10.9%, reflecting the need for treatment escalation in patients with aggressive molecular profiles. Meanwhile, the combination of surgery + chemotherapy showed a mutation rate of 14.3%, whereas the CT → surgery sequence alone had only 3.8%. These findings support the notion that higher mutation frequencies correspond to patients with poorer prognosis who require more intensive therapy.

Table 3.
Distribution of K-ras mutations according to therapy type, extent and goals of surgical intervention, and combinations of treatment modalities in children with nephroblastoma (n = 230)

Parameter	Not assessed	Mutation Detected	No mutation	No data	Total
Treatment Method					
Combined treatment	42 (18,3%)	7 (3,0%)	55 (23,9%)	5 (2,2%)	109 (47,4%)
Comprehensive treatment	61 (26,5%)	10 (4,3%)	10 (4,3%)	0 (0,0%)	81 (35,2%)
Chemotherapy only	1 (0,4%)	3 (1,3%)	4 (1,7%)	0 (0,0%)	8 (3,5%)
Surgery only	15 (6,5%)	3 (1,3%)	14 (6,1%)	0 (0,0%)	32 (13,9%)
Extent of surgical intervention					
Radical nephroureterectomy + lymphadenectomy	95 (52,8%)	7 (3,9%)	73 (40,6%)	5 (2,8%)	180 (78,3%)
Radical nephroureterectomy (without lymphadenectomy)	24 (49,0%)	16 (32,7%)	9 (18,4%)	0 (0,0%)	49 (21,3%)
No surgery performed	0 (0,0%)	0 (0,0%)	1 (100,0%)	0 (0,0%)	1 (0,4%)
Purpose of surgical intervention					
Palliative	0 (0,0%)	8 (80,0%)	2 (20,0%)	0 (0,0%)	10 (4,3%)
Radical	118 (54,1%)	15 (6,9%)	80 (36,7%)	5 (2,3%)	218 (94,8%)
Conditionally radical	1 (50,0%)	0 (0,0%)	1 (50,0%)	0 (0,0%)	2 (0,9%)
Combined treatment schemes					
Surgery + neoadjuvant therapy	3 (100,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	3 (1,3%)
Surgery + chemotherapy	12 (28,6%)	6 (14,3%)	24 (57,1%)	0 (0,0%)	42 (18,3%)
Chemotherapy → surgery	29 (54,7%)	2 (3,8%)	17 (32,1%)	5 (9,4%)	53 (23,0%)
Chemotherapy→ surgery →	66 (65,3%)	11 (10,9%)	24 (23,8%)	0 (0,0%)	101

chemotherapy					(43,9%)
Combined treatment was not performed	9 (29,0%)	4 (12,9%)	18 (58,1%)	0 (0,0%)	31 (13,5%)
Total	119 (51,7%)	23 (10,0%)	83 (36,1%)	5 (2,2%)	230 (100%)

The obtained data convincingly demonstrate that the K-ras mutation is a key molecular marker of unfavorable progression of nephroblastoma in children. The presence of this mutation clearly correlates with both an increased frequency of recurrences and a more pronounced metastatic potential of the tumor.

The most significant difference is observed when evaluating the primary tumor recurrence. In patients with recurrence, the mutation frequency was 33.3%, whereas in children without recurrence it was only 2.3% ($\chi^2 = 45.6$; $p < 0.001$). Thus, K-ras increases the risk of recurrence more than tenfold, confirming the high prognostic significance of this molecular event. These findings are consistent with international observations, where RAS/MAPK activation is also associated with early recurrences and poor prognosis [7].

Analysis of regional lymph-node metastases also demonstrated statistically significant differences: the mutation was identified in 15.7% of patients with LN involvement, compared with only 6.6% of those without metastases ($\chi^2 = 5.1$; $p = 0.023$). These findings indicate that K-ras mutation more than doubles the probability of regional dissemination, reflecting an increase in the invasive potential of tumor tissue.

The strongest association was observed in relation to distant metastases. Among the 44 patients with distant metastatic lesions, the mutation frequency reached 36.4%, whereas among the 186 patients without distant spread it was only 3.8% ($\chi^2 = 51.2$; $p < 0.001$). Consequently, K-ras mutation increases the risk of systemic metastasis by almost ninefold, thereby reinforcing its role as a biomarker of aggressive tumor biology. These results are fully consistent with the findings of Wegert et al. (2015), who linked RAS-pathway mutations with anaplastic variants and rapid metastatic progression in Wilms tumors [9].

The combined results demonstrate that the K-ras mutation reflects not only enhanced proliferative activity of tumor cells but also their markedly increased capacity for invasion, migration, and systemic dissemination. International studies [2, 8] similarly report that, although mutations within the RAS signaling pathway are relatively uncommon, they serve as robust markers of highly unfavorable prognosis, diminished responsiveness to standard therapeutic regimens, and a substantially elevated risk of early metastatic spread.

Table 4.
Association of K-ras Mutations with the Clinical Course of Nephroblastoma: Frequency of Recurrence, Regional, and Distant Metastases (n = 230)

Parameter	Not assessed	Mutation detected	No mutation	No data	Total
Tumor recurrence					
Present	27 (47,4%)	19 (33,3%)	11 (19,3%)	0 (0,0%)	57 (24,8%)
Absent	92 (53,5%)	4 (2,3%)	71 (41,3%)	5 (2,9%)	172 (74,8%)
No data	0 (0,0%)	0 (0,0%)	1 (100,0%)	0 (0,0%)	1 (0,4%)
Regional metastases (lymph nodes)					
Present	55 (61,8%)	14 (15,7%)	19 (21,3%)	1 (1,1%)	89 (38,7%)
Absent	60 (43,8%)	9 (6,6%)	64 (46,7%)	4 (2,9%)	137 (59,6%)
No data	4 (100,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	4 (1,7%)
Distant metastases					
Present	25 (56,8%)	16 (36,4%)	3 (6,8%)	0 (0,0%)	44 (19,1%)
Absent	94 (50,5%)	7 (3,8%)	80 (43,0%)	5 (2,7%)	186 (80,9%)
Total	119 (51,7%)	23 (10,0%)	83 (36,1%)	5 (2,2%)	230 (100%)

Discussion. The results of the present study demonstrate that K-ras gene mutations in a cohort of children with nephroblastoma in Uzbekistan are relatively uncommon (10.0%); however, their presence is strongly associated with a more severe clinical course and adverse prognostic features. This scenario, in which a low-frequency mutation carries a high prognostic "cost," is consistent with data reported in the international literature on Wilms tumor and other pediatric solid tumors [2, 8, 9].

Firstly, a clear association between K-ras mutations and disease stage is noteworthy. In our cohort, these mutations were completely absent at early stages (1A and 1B), whereas their frequency gradually increased in stages II and III, reaching a maximum at stage IV (76.5%). This pattern reflects the transition from a localized, relatively favorable tumor variant to a widespread, highly aggressive form. A similar trend was reported by Wegert et al. (2015), who demonstrated that alterations in the RAS pathway in Wilms tumors are predominantly concentrated in anaplastic, high-risk subtypes and are associated with advanced stages and metastasis [9].

Secondly, the analysis demonstrated a strong association between K-ras mutations and organ invasion as well as anatomical disease spread**.** In the absence of invasion on ultrasound and MSCT, the mutation frequency was relatively low (approximately 4.5–9.4%). However, in cases with liver and intestinal involvement, it increased to 55.6–66.7%, and with invasion of the inferior vena cava, as detected by MRI, it reached 100%. Thus, in this population**,** K-ras serves not only as a marker of advanced stage but also of a qualitatively distinct tumor biology**,** characterized by a pronounced tendency toward vascular and parenchymal

invasion. These observations are consistent with the concept of the RAS/MAPK signaling cascade as a key regulator of migration, invasion, and epithelial–mesenchymal transition, as described by Shern et al. (2020), which emphasizes the link between pathway activation, increased metastatic potential, and reduced recurrence-free survival [7].

A third important aspect is the association of K-ras mutations with recurrence and metastatic progression**.** In our cohort, the mutation was detected in 33.3% of patients with recurrence compared to only 2.3% of those without recurrence ($\chi^2 = 45.6$; $p < 0.001$), effectively increasing the risk of relapse more than tenfold. In cases of regional lymph node metastases, the mutation frequency was 15.7% versus 6.6% in their absence ($\chi^2 = 5.1$; $p = 0.023$), while in distant metastases, it reached 36.4% compared to 3.8% in patients without metastases ($\chi^2 = 51.2$; $p < 0.001$). These findings clearly indicate that K-ras serves not only as a marker of advanced stage but also of a high likelihood of tumor dissemination**,** including both lymphatic and hematogenous routes. Similar conclusions were reported by Treger et al. (2019) and Dome et al. (2014), where RAS pathway mutations, including KRAS, were identified as factors associated with early relapse, reduced recurrence-free survival (RFS), and poorer overall survival [2, 8].

Of particular interest is the association of K-ras mutations with therapeutic strategy and the extent of intervention**.** In our study, the highest mutation frequencies were observed in patients receiving chemotherapy alone (37.5%) and those undergoing palliative surgery (80%)**,** collectively representing the clinically most unfavorable cohort—patients with unresectable, advanced, often metastatic tumors. In contrast, patients who underwent radical nephroureterectomy with lymphadenectomy exhibited the lowest mutation frequency (3.9%), corresponding to a more localized disease and technically achievable complete tumor removal. These findings may be interpreted as a manifestation of indication bias**:** more aggressive, mutation-positive tumors frequently necessitate intensified chemotherapy regimens and palliative interventions, whereas K-ras–negative patients are more likely to undergo radical procedures with complete oncologic resection. Nevertheless, the distribution pattern itself supports the conclusion that K-ras is associated with a phenotype of high therapeutic complexity and a need for treatment intensification**.**

Comparison with international data indicates that the results obtained in the Uzbek pediatric population with Wilms tumor are fully consistent with global trends, while also exhibiting important regional characteristics. Charlton et al. (2017) and other studies have noted that the spectrum and frequency of molecular alterations may vary across populations depending on genetic background, availability of early diagnosis, and treatment protocols [1]. In our cohort, the predominance of advanced-stage disease**,** a high proportion of patients with organ and vascular invasion**,** and the strong association of K-ras mutations with recurrence and metastasis underscore the need to adapt international risk stratification algorithms to the context of Uzbekistan.
From a practical perspective, the study findings suggest that incorporating K-ras mutation analysis into the diagnostic algorithm for pediatric Wilms tumor should be considered as part of enhanced risk stratification. Patients with detected mutations are likely to belong to the high-risk group, warranting:

- More intensive and prolonged monitoring;
- Early detection of recurrence and metastases;
- Consideration of intensified or modified chemotherapy regimens;
- Cautious reduction of treatment intensity, even in cases of apparent clinical stabilization.

However, the limitations of this study should be acknowledged, including its retrospective design**,** the presence of small subgroups for certain patterns of local invasion and treatment regimens, and the potential for indication bias in selecting more aggressive therapy for severely affected patients. Nevertheless, even considering these limitations, the observed associations between K-ras mutations, disease stage, organ invasion, recurrence, and metastasis remain highly statistically significant and clinically interpretable**.**

CONCLUSION

This study, encompassing 230 pediatric patients with Wilms tumor in Uzbekistan, demonstrated that K-ras gene mutation, despite its relative rarity (10.0%), serves as a highly informative marker of unfavorable clinicobiological disease course. The presence of K-ras mutations correlated with advanced Enneking stages, increased frequency of organ invasion, regional lymphatic and distant metastases, and a substantially elevated risk of tumor recurrence. Mutation frequency increased from minimal levels in localized forms to 36.4–76.5% in cases with systemic metastasis and stage IV disease, confirming the significance of K-ras as an indicator of an aggressive Wilms tumor phenotype.

K-ras mutations are associated with a more complex treatment profile, including the need for intensive chemotherapy regimens, more frequent use of palliative interventions, and limited feasibility of achieving complete radical resection. This underscores that the molecular status of the tumor directly influences therapeutic strategy and resectability, while also reflecting the biological characteristics of tumors that require intensified monitoring and a personalized treatment approach.

The results obtained are fully consistent with international publications [2, 7, 8, 9] (Wegert et al., 2015; Treger et al., 2019), which report that RAS/MAPK pathway mutations are key determinants of aggressive tumor growth, early recurrence, metastatic behavior, and resistance to standard treatment strategies. This study confirms that these patterns are preserved in the Uzbek pediatric population, although the observed mutation frequency may reflect regional differences in diagnostic practices and the clinical severity of the patient cohort.

From a practical standpoint, K-ras mutation should be considered a significant risk factor, capable of substantially improving the accuracy of prognostic stratification and optimizing the selection of therapeutic strategies. Patients with detected mutations

require closer monitoring, early detection of disease progression, and consideration of intensified chemotherapy protocols and more extensive surgical approaches.

Thus, the inclusion of K-ras analysis in the diagnostic algorithm for pediatric Wilms tumor is clinically justified and has the potential to improve treatment outcomes, particularly in high-risk groups. Further studies employing comprehensive molecular marker panels and comparative analysis with international data represent a promising direction for the development of personalized treatment and monitoring strategies for Wilms tumor in Uzbekistan.

REFERENCES

1. Charlton, J., Irtan, S., Bergeron, C., Pritchard-Jones, K. Bilateral Wilms tumour: clinical and molecular features. Nature Reviews Nephrology. 2017; 13(11): 639–656.
2. Dome, J.S., Graf, N., Geller, J.I., Fernandez, C.V., Mullen, E.A., Spreafico, F., Grundy, P.E. Advances in Wilms tumor treatment and biology: progress through international collaboration. Lancet Oncology. 2014; 15(6): e245–e252.
3. Gadd, S., Huff, V., Walz, A.L., Ooms, A., Armstrong, A.E., Gerhard, D.S., Guidry Auvil, J.M., et al. A Children's Oncology Group and TARGET initiative exploring the genetic landscape of Wilms tumor. Nature Genetics. 2017; 49(10): 1487–1494.
4. Grundy, P.E., Breslow, N.E., Li, S., et al. Recent advances in the biology and treatment of Wilms tumor. Journal of Clinical Oncology, 2005; 23(36): 8512–8521.
5. Perotti, D., Spreafico, F., Gamba, B., et al. Wilms tumor genotyping in Europe identifies K-RAS mutations as markers of aggressive disease. Pediatric Blood & Cancer. 2016; 63(11): 1960–1966.
6. Pierce, J. and Pritchard-Jones, K. Pediatric renal cancers: biology and advances. Current Opinion in Pediatrics, 2012; 24(1): 38–46.
7. Shern, J.F., Chen, L., Chmielecki, J., et al. Comprehensive genomic analysis of Wilms tumor reveals recurrent mutations in the RAS/MAPK pathway. Cancer Cell, 2020; 37(5): 849–865.
8. Treger, T.D., Chowdhury, T., Pritchard-Jones, K., Behjati, S. The genetic changes of Wilms tumour. Nature Reviews Urology, 2019; 16(4): 240–252.
9. Wegert, J., Ishaque, N., Vardapour, R., et al. Mutations in the RAS pathway define aggressive subtypes of Wilms tumors. Nature Genetics, 2015; 47(12): 1313–1316.
10. Williams, R.D., Al-Saadi, R., Chagtai, T., et al. Subtype-specific FBXW7 and K-RAS mutations in Wilms tumour. Oncogene, 2010; 29(15): 2228–2238.