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Single Centre Experience in Neuroblastoma: Surgical Results and Complications

Nöroblastomda Tek Merkez Deneyimi: Cerrahi Sonuçlar ve Komplikasyonlar

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Abstract

Aim: Neuroblastoma (NB) is an embryonal neuroendocrine tumor of the peripheral nervous system. It is the most common extracranial solid tumor of childhood and the most common in the first year of life.It has a variable course ranging from a benign course to a fatal disease.

Material and Method: Forty patients under the age of 18 who underwent surgical resection in our center due to neuroblastoma between January 2012 and December 2021 were included in to the study. Demographic data of the patients, preoperative cross-sectional and functional imaging, surgical procedures, surgical complications and pathological staging were analyzed retrospectively.

Results: In this retrospective study, 48 patients were analyzed. Of 48 patients 52.5% were male and 47.5% were female. palpable abdominal mass detected in 82.5% of the patients. 30 patients were neuroblastoma, 10 patients were ganglioneuroblastoma, and 8 patients were ganglioneuromas. Eight patients with ganglioneuroma were excluded from the study. Analysis was performed among 40 patients.

Conclusion: NB is heterogeneous in clinical behavior. It is treated by the pediatric surgeon with minimal complications, taking into account the stage of the disease, the age of the patient, and risk factors. Since the tumor originates from the sympathetic nervous system and invades surrounding large vessels and surrounding tissues, aggressive chemotherapy and local regional radiotherapy may be required after surgery. It may be possible to avoid serious complications by customizing the surgery.

Keywords: Neuroblastoma, surgery, clinical behaviour

Öz

Amaç: Nöroblastom (NB), periferik sinir sisteminin embriyonal nöroendokrin tümörüdür. Çocukluk çağının en sık görülen ekstrakraniyal solid tümörüdür ve yaşamın ilk yılında en sık görülür. İyi huylu bir seyirden ölümcül bir hastalığa kadar değişen değişken bir seyir gösterir.

Gereç ve Yöntem: Ocak 2012 ile Aralık 2021 arasında merkezimizde nöroblastom nedeniyle cerrahi rezeksiyon geçiren 18 yaş altı kırk hasta çalışmaya dahil edildi. Hastaların demografik verileri, ameliyat öncesi kesitsel ve fonksiyonel görüntüleme, cerrahi prosedürler, cerrahi komplikasyonlar ve patolojik evreleme retrospektif olarak analiz edildi.

Bulgular: Bu retrospektif çalışmada 48 hasta analiz edildi. 48 hastanın %52,5'i erkek ve %47,5'i kadındı. Hastaların %82,5'inde elle muayene edilebilen abdominal kitle tespit edildi. 30 hasta nöroblastoma, 10 hasta ganglionöroblastoma ve 8 hasta ganglionöroma idi. Ganglionöroma olan sekiz hasta çalışmadan hariç tutuldu. Analiz 40 hasta arasında yapıldı.

Sonuç: NB klinik davranışta heterojendir. Hastalığın evresi, hastanın yaşı ve risk faktörleri dikkate alınarak, pediatrik cerrah tarafından minimal komplikasyonlarla tedavi edilir. Tümör sempatik sinir sisteminden kaynaklandığı ve çevredeki büyük damarları ve çevre dokuları istila ettiği için, ameliyattan sonra agresif kemoterapi ve lokal bölgesel radyoterapi gerekebilir. Ameliyatı kişiselleştirerek ciddi komplikasyonlardan kaçınmak mümkün olabilir.

Anahtar Kelimeler: Nöroblastom,, cerrahi, klinik davranış

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INTRODUCTION

Neuroblastoma (NB) is an embryonal neuroendocrine tumour of the peripheral nervous system, representing the most common extracranial solid tumour of childhood and frequently diagnosed within the first year of life.[1-3] It presents a highly variable clinical course, ranging from spontaneous regression to widespread metastatic disease that is unresponsive to treatment.[4] NB contributes to approximately 15% of all childhood cancer-related deaths.[5] While neuroblastoma can arise anywhere along the sympathetic nervous system pathway, the majority of tumours originate in the adrenal glands.[6,7]

The prognosis of neuroblastoma is remarkably diverse, influenced by several factors including the patient's age at diagnosis, disease stage, histopathological features (e.g., differentiation, presence of mitosis-karyorrhexis index), and numerous biological markers.[8] Approximately 50% of patients present with metastatic disease at the time of diagnosis, with common sites of metastasis including bone, bone marrow, and lymph nodes.[9] The most frequent presenting symptom of neuroblastoma is a painless abdominal mass. Other symptoms may arise from primary tumour compression, sequelae of metastatic disease, or paraneoplastic syndromes.

Accurate evaluation of the primary tumour typically involves cross-sectional imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI) to assess the extent of local invasion, relationship with critical vascular structures (image-defined risk factors, IDRFs), and the presence of distant metastases. Functional imaging techniques, including Metaiodobenzylguanidine (MIBG) scintigraphy and 18-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT), are vital for detecting metastatic disease, defining tumour burden, and monitoring treatment response. These methods are particularly useful due to the high metabolic activity of tumour cells, often quantified by the maximum standardised uptake value (SUVmax).[10]

Neuroblastoma Staging System

Neuroblastoma staging is primarily guided by the International Neuroblastoma Risk Group (INRG) Staging System, which incorporates Image-Defined Risk Factors (IDRFs).[11,12] IDRFs are crucial imaging features that predict the likelihood of complete surgical resection and are fundamental in determining the initial risk stratification. Patient treatment strategies are primarily determined by these risk groups, which integrate stage, age, and biological factors.

Diagnosis is typically confirmed by biopsy, often sufficient on its own. Alternatively, the diagnosis can be established based on characteristic bone marrow involvement alongside elevated urinary catecholamine levels (vanillylmandelic acid. [VMA] and homovanillic acid.[HVA]).[13]

Effective neuroblastoma treatment hinges on proper risk stratification. Surgical resection of the primary tumour is the standard approach for very low and low-risk patients. Moderate-risk patients typically receive neoadjuvant chemotherapy (CT) followed by surgical resection to improve resectability and minimise complications.[14] Management of high-risk patients involves a comprehensive, multimodal approach, integrating chemotherapy, aggressive surgical resection, locoregional radiotherapy, autologous stem cell transplantation, and immunotherapy.[15,16]

In this study, we aimed to evaluate the correlation between pre-operative PET-CT SUVmax values and the percentage of viable tumour tissue in histopathology preparations following neoadjuvant treatment, and their combined effect on survival outcomes. We also analysed the surgical results and complication rates in our single-centre experience.

MATERIAL AND METHOD

The study was carried out with the permission of Adana City Training and Research Hospital Ethics Committee (Date: 24.03.2022, Decision No: 102/1849). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective study included 40 patients under 18 years of age who underwent surgical resection for neuroblastoma or ganglioneuroblastoma at Adana City Training and Research Hospital between January 2012 and December 2021. Patients primarily diagnosed with ganglioneuroma (n=8) were excluded from the analysis to ensure focus on the more malignant spectrum of neuroblastic tumours, as ganglioneuromas generally follow a benign course and often do not require aggressive intervention beyond primary resection.

Data Collection

Demographic data, including age at diagnosis and gender, were collected. Pre-operative cross-sectional imaging (CT, MRI) and functional imaging (MIBG, PET-CT) reports were reviewed to assess tumour size, location, extent of local invasion, and the presence of distant metastases. Image-defined risk factors (IDRFs) were specifically assessed based on the INRG criteria to evaluate tumour relationship with critical vascular structures and organs. Surgical procedures were meticulously reviewed, including the type of surgical approach (e.g., open laparotomy, thoracotomy), the extent of resection (total vs. subtotal), and any specific surgical challenges encountered. Intra-operative complications were documented. Post-operative care protocols, including the administration of adjuvant chemotherapy or radiotherapy, were also recorded. Pathological staging was performed according to the International Neuroblastoma Risk Group (INRG) Staging System. The rationale for dividing patients into age groups (≤24 months and >24 months) was based on established prognostic factors in neuroblastoma, where younger age generally correlates with a more favourable outcome. Similarly, the percentage of viable tumour tissue in post-neoadjuvant pathology specimens was categorised as ≤15% or >15%, a cut-off often used in literature to indicate response to chemotherapy and its potential prognostic implications.

Surgical Technique and Complication Classification

All surgical procedures were performed by experienced paediatric surgeons. The specific surgical technique employed was individualised based on tumour location, size, and its relationship to vital structures as determined by pre-operative imaging and IDRF assessment. For adrenal tumours, a transperitoneal approach was typically used. For paravertebral tumours, a posterior or postero-lateral approach might be utilised. Meticulous dissection was performed to preserve vital structures and achieve maximal safe resection. Intra-operative complications (e.g., significant haemorrhage, organ injury) and post-operative complications were prospectively recorded in the patient files and were retrospectively classified using the Clavien-Dindo Classification System[17,18] This system provides a standardised grading for surgical complications, allowing for objective assessment of morbidity. Post-operative care included routine monitoring, pain management, and nutritional support. Decisions regarding adjuvant chemotherapy or radiotherapy were made by a multidisciplinary tumour board, involving paediatric oncologists, radiation oncologists, and paediatric surgeons, based on the patient's risk stratification (INRG risk group), histopathology, and molecular markers (though molecular markers were not analysed in this specific study).

Statistical Analysis

For statistical analysis, SPSS (Statistical Package for the Social Sciences, Chicago, IL) for Windows version 25.0 was used. Descriptive statistics were presented as frequencies, percentages, medians, and ranges. Survival analyses were performed using the Kaplan-Meier method, and comparisons between groups were made using the log-rank test. Mean survival times, along with their 95% Confidence Intervals (CI), were calculated. To assess the predictive accuracy of potential biomarkers (NSE, Ferritin, VMA, PET SUV-max, and percentage of viable tumour tissue), Receiver Operating Characteristic (ROC) analysis was performed. Optimal cut-off values were determined based on Youden's index, and the Area Under the Curve (AUC), along with 95% Confidence Intervals (CI) for AUC, sensitivity, and specificity, were reported. Hazard Ratios (HR) for relevant prognostic factors were estimated using Cox proportional hazards regression models. A p-value of less than 0.05 was considered statistically significant.

RESULTS

In this retrospective study, data from 40 patients with neuroblastoma or ganglioneuroblastoma were analysed. Of these, 21 patients (52.5%) were male and 19 (47.5%) were female. A palpable abdominal mass was the presenting symptom in 33 patients (82.5%). Histopathological analysis revealed 30 cases of neuroblastoma (75.0%) and 10 cases of ganglioneuroblastoma (25.0%). Eight patients initially included with ganglioneuroma were excluded from the final analysis as per the revised study design.

Patients were stratified into two age groups for survival analysis: 15 patients (37.5%) were aged 0-24 months, and 25 patients (62.5%) were over 24 months. The geographical origin indicated that 25 patients (62.5%) were from Türkiye and 15 (37.5%) were from Syria. Mass localisations included 22 right-sided (55.0%), 16 left-sided (40.0%), and 2 paravertebral (5.0%) tumours. At the last follow-up, 13 patients (32.5%) were in remission, 15 (37.5%) were under disease-free follow-up, 11 (27.5%) had expired, and 1 (2.5%) was lost to follow-up due to non-compliance.

Advanced stage disease (Stages 3 and 4 according to INRG criteria) was observed in 72.5% of patients (7 in Stage 3, 22 in Stage 4). There were 4 patients with Stage 4S disease. Neoadjuvant chemotherapy was administered to 30 patients (75%). Intra-operative assessment revealed local invasion in 19 patients (47.5%). Histopathological subgrouping (based on differentiation) showed 11 poorly differentiated (27.5%), 4 differentiated (10.0%), 2 intermixed (5.0%), 1 intermediate differentiated (2.5%), and 3 undifferentiated (7.5%) tumours. For 19 patients (47.5%), the differentiation status was undefined or not clearly specified in the records.

The median follow-up period for the entire cohort was 29.5 months (range: 2.7-107 months). Overall survival (OS) for the entire cohort was 63.8%. There was no statistically significant difference in OS rates based on gender (males: 64.2%, females: 62.7%; p=0.11).

Survival by Stage

Overall survival rates varied significantly by stage: 100% for early stage (1, 2) and 4S, and 62.2% for advanced stage (3 and 4) (**Figure 1**). In advanced stage tumours, the 1-year survival rate was 77.5%, decreasing to 49.5% at 2 years.

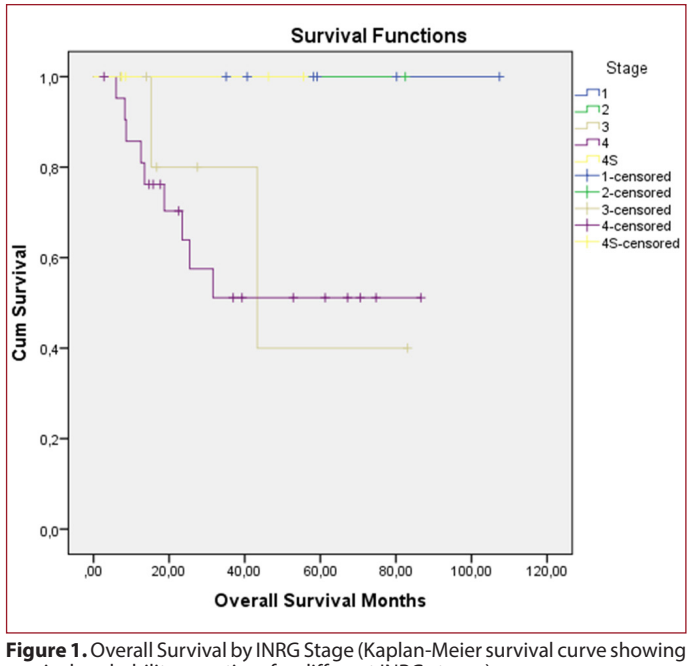

Figure 1. Overall Survival by INRG Stage (Kaplan-Meier survival curve showing survival probability over time for different INRG stages)

Survival by Age Group

The overall survival rate was significantly higher in the group aged ≤24 months (83.3%) compared to the group >24 months (63.8%) (p=0.09). In the group >24 months, 1-year survival was 80.9%, and 2-year survival was 63.8% (**Figure 2**).

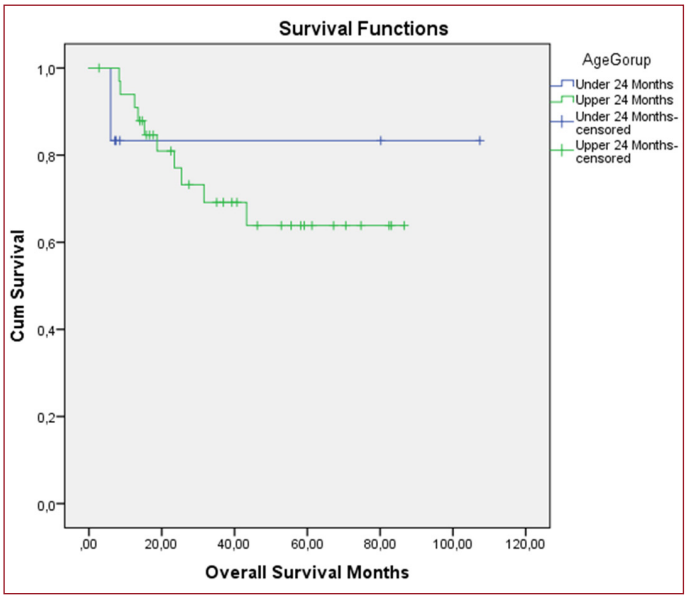

Figure 2. Overall Survival by Age Group (Kaplan-Meier survival curve showing survival probability over time for age groups ≤24 months and >24 months)

Prognostic Value of PET-CT SUVmax

The median PET-CT SUVmax value was 1.8 (range: 0-12). Overall survival was 77.9% in patients with a PET-CT SUVmax value ≤1.8, while it was 27.3% in patients with a value >1.8 (p=0.101). ROC analysis for PET SUV-max as a predictor of survival yielded an AUC of 0.789 (95% CI: 0.654-0.924), with an optimal cut-off value of 2.15, demonstrating a sensitivity of 78% and a specificity of 71%.

Palpable Abdominal Mass

Patients presenting with a palpable abdominal mass had an overall survival rate of 71.9%, significantly higher than those without a palpable mass (25.0%) (p=0.005).

Viable Tumour Tissue after Neoadjuvant Treatment

The rate of viable tumour tissue in pathology preparations was analysed for 22 patients who received neoadjuvant treatment. In the group with ≤15% viable tumour tissue, survival was 62.3%, while it was 40.4% in the group with >15% viable tumour tissue (p=0.93), though this difference was not statistically significant.

Local Invasion and Surgical Extent

In terms of local invasion observed during surgery, overall survival was 50.2% in patients with local invasion compared to 77.3% in those without local invasion (p=0.191). Survival analysis based on the extent of surgical resection revealed an overall survival rate of 79.6% for total resections and 43.44% for subtotal resections (p=0.257).

Intra-operative and Post-operative Complications

Surgical complications were observed in 5 patients (12.5%). Specifically, 2 patients (5.0%) experienced significant intra-operative bleeding requiring blood transfusion (Clavien-Dindo Grade II), and 3 patients (7.5%) developed post-operative wound infection (Clavien-Dindo Grade I) that resolved with conservative management. No Clavien-Dindo Grade III or higher complications were observed.

Table 1. Demographic and Clinicopathological Features of Patients

Feature	Frequency (n)	Percentage (%)
Gender		
Male	21	52.5
Female	19	47.5
Origin		
Türkiye	25	62.5
Syria	15	37.5
Diagnosis		
Ganglioneuroblastoma	10	25.0
Neuroblastoma	30	75.0
Final Condition		
Remission	13	32.5
Disease-free follow-up	15	37.5
Ex (Expired)	11	27.5
Missing	1	2.5
Stage (INRG)		
1	6	15.0
2	1	2.5
3	7	17.5
4	22	55.0
4S	4	10.0
Palpable Abdominal Mass		
Yes	33	82.5
No	7	17.5
Neoadjuvant Treatment		
Yes	30	75.0
No	10	25.0
Local Invasion (Surgical)		
Yes	19	47.5
No	21	52.5
Histopathological Subgroup		
Poorly Differentiated	11	27.5
Undefined	19	47.5
Differentiated	4	10.0
Intermixed	2	5.0
Intermediate Differentiated	1	2.5
Undifferentiated	3	7.5
Tumour Side		
Paravertebral	2	5.0
Right	22	55.0
Left	16	40.0
Median (Min-Max)		
Median follow-up time (months)	29.5 (2.7-107)	
PET-SUV max	1.8 (0-12)	

Table 2. Overall Survival of Patients

Feature	Mean Survival (months)	95% CI (Min-Max)	p-value	Overall Survival (%)
Average Survival	76.9	62.1-91.7		63.8
Gender				
Male	75.2	54.3-96.1	0.110	64.2
Female	64.1	47.6-80.5		62.7
Stage (INRG)				
1	-	-		100.0
2	-	-		100.0
3	-	-		62.2
4	-	-		62.2
4S	-	-		100.0
PET SUVmax				
≤1.8	38.4	31.3-45.4	0.101	77.9
>1.8	28.9	18.6-39.2		27.3
Palpable Abdominal Mass				
Yes	84.0	69.1-98.9	0.005	71.9
No	30.5	4.3-56.7		25.0
Age Group				
≤24 months	90.5	60.2-120.8	0.090	83.3
>24 months	63.3	51.4-75.1		63.8
Local Invasion				
Yes	65.4	42.3-88.5	0.191	50.2
No	67.9	54.9-81.1		77.3
Surgery Extent				
Total	79.7	64.4-94.9	0.257	79.6
Subtotal	43.4	5.2-81.7		43.44

p<0.05, **p<0.001 (Kaplan-Meier – Log-rank test)

DISCUSSION

Neuroblastoma is recognised as the most common malignant abdominal tumour in children.[19] Its clinical progression is highly variable, ranging from spontaneous regression, particularly in certain low-risk subgroups, to aggressive, diffuse metastatic disease that is refractory to treatment.

Patients with Stage 4S neuroblastoma (under 18 months of age with limited metastatic disease) generally exhibit a favourable prognosis, with reported survival rates in the literature ranging from 56% to 90%.[20-21] Our study's finding of 100% overall survival in patients under 24 months with Stage 4S is consistent with the optimistic outcomes often seen in this specific subgroup, further emphasising the importance of age and limited metastatic burden as favourable prognostic indicators.

Surgical resection of the primary tumour remains the cornerstone of treatment, yielding the best results in appropriately selected patients, particularly those with very low and low-risk disease. Patients who receive neoadjuvant chemotherapy before surgical resection or those treated with surgical resection and radiotherapy without preceding chemotherapy may have varied outcomes depending on the risk stratification and tumour biology.[22] Previous studies in some countries have indicated that approximately half of the NB cases detected via catecholamine screening in the first years of life might undergo spontaneous regression, highlighting the biological heterogeneity of this tumour.[23,24]

In our cohort, a high proportion of patients (72.5%) presented with advanced disease, which inherently contributes to the observed lower overall survival rates compared to cohorts dominated by early-stage cases. Consequently, a majority of our patients (75%) underwent surgery after neoadjuvant therapy. The overall survival rate for patients who received surgical resection following neoadjuvant therapy in our study was 63.3%. The optimal timing of surgery in the context of neoadjuvant therapy and its ultimate effect on survival continues to be a subject of debate in the literature. Most NB tumours respond well to chemotherapy, and performing surgery during or after induction chemotherapy often improves resectability by reducing tumour size and mitigating its relationship with adjacent organs and major vessels, thereby facilitating surgery with minimal complications.[25]

Our study also evaluated the impact of the percentage of viable tumour tissue on survival after neoadjuvant treatment, finding that overall survival was 62.3% in patients with ≤15% viable tumour tissue, which decreased to 40.4% in those with >15%. While this trend suggests a potential prognostic role, the difference did not reach statistical significance (p=0.93) in our cohort. This finding aligns with some previous studies that also struggled to demonstrate a statistically significant correlation, while others have reported the prognostic value of residual viable tumour.[26,27] This suggests that larger, multi-institutional studies are needed to establish definitive guidelines for the clinical interpretation of this parameter.

Factors affecting survival in advanced tumours have been extensively evaluated in various series, considering diverse induction treatments, optimal timing of surgery, pre-operative cross-sectional imaging for risk stratification (including IDRFs), individualised surgical approaches, and the use of peri-operative tumour localisation markers for post-resection radiotherapy planning.[26,27] Our findings regarding the impact of palpable abdominal mass and local invasion on survival are consistent with the general understanding that higher tumour burden and local aggressiveness negatively impact prognosis. The significant difference in survival based on the extent of resection (total vs. subtotal) underscores the critical importance of achieving complete surgical removal when clinically feasible.

The Significance of Viable Tumour Tissue Proportion in Neuroendocrine Tumours (NETs)

The proportion of viable tumour tissue remaining after treatment for neuroendocrine tumours (NETs) is considered a crucial parameter in assessing disease progression and prognosis. This ratio is particularly evaluated during pathological examinations following surgical resection or neoadjuvant (pre-operative) therapy, providing critical information for predicting a patient's future risk of recurrence and overall survival.

Neuroendocrine tumours represent a heterogeneous group of neoplasms exhibiting a broad spectrum of biological behaviours. In evaluating treatment response, not only changes in tumour size but also the microscopic cellular response hold significant importance. The percentage of viable tumour tissue reflects the true efficacy of chemotherapy, radiotherapy, or other systemic therapies on the tumour.

Prognostic Prediction: Generally, a lower proportion of viable tumour cells in the resected tumour tissue correlates with a better prognosis and longer disease-free survival. Conversely, a higher proportion of viable tumour tissue usually indicates a poor response to treatment and a greater risk of recurrence.

Assessment of Treatment Response: In patients who have received neoadjuvant therapy, the viable tumour proportion identified in post-surgical pathological examination offers an objective criterion for assessing the efficacy of the administered treatment. This information can guide the determination of adjuvant (post-operative) treatment plans.

Risk Stratification: The viable tumour proportion can be incorporated as an additional prognostic factor into existing risk stratification systems or utilised in the development of new risk models.

In neuroblastoma, the proportion of viable tumour tissue after neoadjuvant chemotherapy is investigated as a prognostic factor. Our article's findings indicated a trend towards higher survival with a viable tumour proportion below 15%, though statistical significance was not achieved (p=0.93). This aligns with the sometimes contradictory or inconclusive findings in the literature on this topic. Some studies suggest that a good pathological response (i.e., a low proportion of viable cells) after neoadjuvant therapy positively impacts survival, especially in high-risk neuroblastoma, while others have not found a statistically significant correlation. These discrepancies may arise from variations in study designs, patient populations, neoadjuvant treatment regimens, and methodologies for determining viable tumour proportion.

Future research should focus on larger, prospective cohort studies and standardised pathological assessment methods to more definitively establish the prognostic value of the viable tumour tissue proportion. Furthermore, evaluating this proportion in conjunction with molecular markers and genetic profiling could offer a more comprehensive approach to risk analysis and treatment personalisation in neuroendocrine tumours.

In the management of neuroendocrine tumours, pathological response parameters such as the viable tumour tissue proportion should be evaluated with a multidisciplinary approach, alongside the tumour's biological characteristics and clinical course. This ensures that patients receive the most appropriate and individualised treatment plan.

The clinical behaviour of neuroblastoma is markedly heterogeneous. Effective management requires a highly individualised approach by a multidisciplinary team, involving paediatric surgeons, oncologists, and radiologists. Treatment decisions are carefully made considering the disease stage, patient age, and specific biological and Image-Defined Risk Factors (IDRFs). Given that the tumour originates from the sympathetic nervous system and frequently invades large surrounding vessels and tissues, aggressive combined modality therapy, including neoadjuvant chemotherapy and locoregional radiotherapy, is often necessary following surgical resection, particularly in high-risk cases. Customising the surgical strategy based on individual patient characteristics and tumour biology is paramount to avoid serious complications and optimise long-term outcomes.

Limitations

This study is limited by its retrospective, single-centre design and relatively small sample size, which may limit the generalisability of our findings. The long study period (2012-2021) might introduce variability in treatment protocols and imaging techniques over time. The lack of detailed molecular biological markers (e.g., MYCN amplification status) for all patients is another limitation, as these are crucial for comprehensive risk stratification and prognosis. While we excluded ganglioneuromas, the inclusion of both neuroblastoma and ganglioneuroblastoma in the primary analysis, despite their distinct pathological features, could introduce some heterogeneity. Future prospective, multi-institutional studies with larger cohorts and comprehensive molecular profiling are needed to validate these findings and further clarify the prognostic significance of various factors, including the percentage of viable tumour tissue and the optimal role of PET-CT SUVmax in clinical decision-making.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Adana City Training and Research Hospital Ethics Committee (Date: 24.03.2022, Decision No: 102/1849).
Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.
Referee Evaluation Process: Externally peer-reviewed.
Conflict of Interest Statement: The authors have no conflicts of interest to declare.
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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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