Rhabdomyosarcoma (RMS), as one of the small blue round cell tumors (SBRCTs), is the most common sarcoma of childhood representing 50.9% of all.\(^1\) It is the second most common head and neck (H&N) malignancy after lymphoma.\(^2\) Rhabdomyosarcoma has a slight male predominance and is usually diagnosed before the age of 10 years; it can also affect older children.\(^3,4\) It has embryonic, alveolar, pleomorphic and spindle cell/sclerosing subtypes.\(^5\) The embryonic subtype affects younger patients and has a good prognosis whereas the alveolar subtype affects older children and has a poor prognosis.\(^3\) The pleomorphic subtype is seen only in adults. Spindle cell/sclerosing subtype is rare and most commonly involves paratesticular and H&N regions.\(^6\)

Head and neck RMSs could be divided into subgroups according to the primary location...
such as parameningeal, nonparameningeal, and orbital RMSs. Parameningeal RMSs arise in regions adjacent to the meninges such as the nasopharynx, parapharyngeal space, masticatory space, nasal/paranasal regions. Therefore, parameningeal RMSs harbor surgical difficulties and have a poor outcome. Non-parameningeal RMSs tend to be superficial.

Signal characteristics of RMS in magnetic resonance imaging (MRI) are not specific; demonstrating intermediate to high signal intensity (SI) on T2 weighted images (WI) and intermediate SI on T1WI compared to muscle. Head and neck RMSs may show various enhancement patterns; most are reported to enhance heterogeneously. Non-enhancing areas corresponding to necrosis or hemorrhage may be seen. Similar to other SBRTs including lymphoma, RMS demonstrates restricted diffusion due to high cellularity.

The imaging characteristics of RMSs, especially parameningeal type, could overlap with the common tumors of the H&N region such as lymphoma and nasopharyngeal carcinoma (NPC) including restriction of diffusion.

The definition of the site of origin and the differentiation of RMS is not frequently problematic when it is localized in striated muscles with distortion of the adjacent tissues. Nevertheless, RMS originates from primitive mesenchymal cells and it can arise anywhere where striated muscle is not normally found. Furthermore, RMSs generally rapidly grow with adjacent tissue infiltration and sometimes it can be difficult to clearly discriminate the tissue compartments on MRI and thus differentiate RMSs using generally known MRI features. Distinguishing these tumors, which is important for determining different treatment management, can be difficult because of the overlapping demographics, tumor location and extent, and imaging features. Our goal was to investigate imaging discriminators that could favor the diagnosis of RMSs over lymphoma and NPC.

Material and Methods

Patients

Institutional Review Board (2020/16-26) approved the study protocol and informed consent was waived by Hacettepe University Institutional Review Board. A retrospective research was performed from July 2014 to June 2020 in Hospital Information System to identify patients with histopathologically proven diagnosis of RMS, lymphoma and NPC. Inclusion criteria were as follows: 1) patients younger than 18 years old; 2) histopathologically proven diagnosis of RMS, suprathyroid lymphoma and NPC; 3) patients with an MRI scan before biopsy and treatment. Exclusion criteria were as follows: 1) orbital lesions (mainly affecting orbits); 2) too small masses with the longest diameter < 1cm on axial T2WI, to ensure an appropriate localization of region of interest (ROI); 3) images with prominent distortion or susceptibility artifacts; 4) MR examination in which diffusion-weighted imaging was not performed.

Imaging

All MR examinations were performed on 1.5 T scanners (Achieva, Philips Healthcare, Best, the Netherlands; Signa, GE Healthcare, Milwaukee, Wisconsin; and Symphony, Siemens, Erlangen, Germany). The imaging protocol was the same for all scans and included coronal, sagittal, and axial T1WI, coronal short tau inversion recovery (STIR) image, axial T2WI with fat saturation, single shot echo planar imaging (EPI) DWI and post-contrast fat-saturated axial and coronal T1WI. Imaging parameters were; T1WI (TR/TE: 410-640/7-15 ms, 3.5-4 mm section thickness, NEX: 1-2, FA: 90°), coronal STIR (TR/TE: 2353-6200/37-60 ms, 3.5-4 mm section thickness, NEX: 1-2, FA: 90°), axial fat-saturated T2WI (TR/TE: 2320-5000/83-90 ms, 3-4 mm section thickness, NEX: 1-2, FA: 90°), DWI (TR/TE: 3400-5674/75-94 ms, and 3-4 mm section thickness, NEX: 2-4, FA: 90°). Post-contrast T1W images were obtained after IV injection of 0.1 mmol/kg gadolinium-based contrast agent.
Single-shot echo-planar imaging (SS-EPI) technique was used for DWI acquisition and performed before the contrast media injection. DWI was acquired with three b-value with values of 0, 500, and 1000 s/mm$^2$. Apparent diffusion coefficient (ADC) maps were automatically generated.

**Image Evaluation**

Qualitative Analysis was performed on hospital Picture Archiving and Communication System (PACS) in consensus by two neuroradiologists (SP and EB, 4- and 7-year experience in H&N radiology) blinded to histopathologic diagnosis. Tumor localization and affected spaces were noted. If more than one space were infiltrated by the tumor, involvement was defined as multicompartment involvement. The presence of skull base invasion, intracranial extension, and retropharyngeal and/or cervical lymphadenopathy were also noted. Distant organ metastasis/involvement was determined by cross-sectional imaging (CT, MRI and PET-CT) findings.

Signal characteristics and post-contrast enhancement patterns of tumors were evaluated. Tumor necrosis was defined as the presence of high SI on T2WI, low SI on T1WI, lack of enhancement with high ADC levels$^{10,16,17}$. The quantitative analysis was performed on hospital PACS independently by two neuroradiologists (SP and EB) blinded to histopathologic diagnosis. ADCs of the tumors were measured by using both the small sample and single slice method. In the small sample method, three separate circular ROI’s (with an area of 1cm$^2$) were placed on the darkest area on ADC maps, which probably represent the highest cellular activity within the tumor. The necrotic areas were avoided. The mean values obtained from these measurements were defined as ADC$_{lesion}$. In the single slice method, a freehand ROI was drawn outlining the largest cross-sectional area of the tumor (ADC$_{area}$) from a single slice.

**Statistics Analysis**

IBM Statistics 23.0 was used for statistical analysis and the $p$ value of $<0.05$ was considered significant. Categorical variables were presented as count and percentage. Mean and standard deviations (SD) and median (Min-Max) values were given for variables with normal distribution and without normal distribution, respectively. For comparison of three groups, the Kruskal Wallis test was used. Pairwise comparisons were made to determine the relationship between groups. The intra-class correlation coefficient (ICC) was calculated for the assessment of inter-observer agreement. In terms of agreement, ICC value was interpreted as poor ($< 0.50$), moderate (0.50-0.75), good (0.75-0.90), or excellent (>0.90).

**Results**

The study included 12 patients with RMS (9 parameningeal and 3 nonparameningeal), 14 patients with lymphoma and 16 patients with NPC. A flow chart of the patients enrolled in the study is shown in Figure 1. Seven patients (58.3%) had embryonic, two patients (16.7%) had spindle cell/sclerosing and one patient (8.3%) had alveolar histopathologic subtypes of RMS. In two patients with RMS histopathologic subtype was undetermined.

Demographic features of the patients, tumor localization and extent, signal and enhancement characteristics are summarized in Table I.

The median age of patients with NPC was significantly higher than the median age of patients with RMS and lymphoma ($p<0.001$ and $p=0.002$). There was no significant difference between RMS and lymphoma cohorts on age ($p>0.05$).

Multicompartment involvement was frequent in both NPC (seen in all cases) and RMS (75%) cohorts. Nasopharyngeal carcinoma showed significantly more multicompartment involvement than lymphoma ($p=0.003$) and RMS...
There was no significant difference between RMS and lymphoma in terms of multicompartment involvement (p=0.34).

Nasopharyngeal ± parapharyngeal involvement was found as 58.3% in RMS and 57.1% in lymphoma (Fig. 2). Skull base involvement, cervical and retropharyngeal lymphadenopathy were more common in patients with NPC (p<0.001 and p<0.05). In three RMS cases (25%) and in four lymphoma cases (28.6%) tumors tend to encircle vascular structures.

Distant organ metastasis/involvement was seen in five lymphoma patients (p=0.014). Five patients had intraabdominal lymphadenopathy (35.7%), four patients had splenic involvement (28.5%), three patients had hepatic involvement (21%), two patients had intrathoracic lymphadenopathy (14%), two patients had bone marrow involvement (14%). Kidney (n=1), pancreas (n=1) and axillary lymph nodes (n=1) were rare involvement areas.

T2 signal homogeneity was significantly more common in lymphoma (p<0.01). RMS was more heterogeneous in T2 images compared to lymphoma (p=0.014). RMS and NPC were not different in terms of T2 homogeneity (p>0.05). RMS lesions showed a significantly higher ratio of heterogeneous enhancement than lymphoma and NPC (p<0.001). A total of seven patients (six embryonic and one spindle cell/sclerosing subtypes) with RMS (58.3%) had imaging findings compatible with tumor necrosis. None of the lymphoma and NPC had necrotic component (p<0.001) (Fig. 3).

The mean values of $ADC_{\text{lesion}}$ and $ADC_{\text{area}}$ for each group and the results of the Kruskal Wallis test are summarized in Table II. The mean ADC values were significantly different between groups (p≤0.001).

Through further evaluation with pairwise comparisons, the mean ADC values ($ADC_{\text{lesion}}$ and $ADC_{\text{area}}$) were found to be significantly
Table I. Summary of demographics, pathologic and imaging characteristics.

|                      | RMS n:12 | Lymphoma n:14 | Nasopharyngeal ca. n:16 | p value |
|----------------------|----------|----------------|-------------------------|---------|
| Gender (F/M)         | 5/7      | 1/13           | 2/14                    | 0.088   |
| Median age (years)   | 4        | 7              | 14                      | <0.001* |
| (min-max)            | (2-17)   | (2-15)         | (11-18)                 |         |
| Multicompart involvement | 75%    | 57.1%           | 100%                    | 0.008*  |
| Nasopharynx±parapharyngeal involvement | n:9  | n:8            | n:16                    | 0.004*  |
| Skull base involvement | n:7         | n:8            | n:16                    | <0.001* |
| Intracranial extension | n:1     | n:2            | n:5                     | 0.332   |
| Distant metastasis/distant organ involvement | n:5 | 35.7% | n:5                     | 0.014*  |
| Lymphadenopathy (cervical/retropharyngeal) | n:5 | n:8 | n:15                    | 0.018*  |
| T2 signal intensity  |          |                |                         |         |
| Homogeneous          | 16.7%    | 64.3%          | 18.8%                   |         |
| Heterogeneous        | 83.3%    | 35.7%          | 81.2%                   | 0.006*  |
| Enhancement a         |          |                |                         |         |
| Homogeneous          | 16.7%    | 78.6%          | 81.2%                   | <0.001* |
| Heterogeneous        | 83.3%    | 21.4%          | 12.5%                   |         |
| Presence of necrosis | 58.3%    | 0%             | 0%                      | <0.001* |

* Post-contrast T1WI was not available in a nasopharyngeal carcinoma patient.
*Statistically significance
RMS: Rhabdomyosarcoma

Table II. The comparison of ADC measurements of groups with Kruskal-Wallis Test.

|                      | RMS          | Lymphoma     | Nasopharyngeal ca. | p value |
|----------------------|--------------|--------------|--------------------|---------|
| Mean ADC_{lesion} (x10^-3mm^2/s) | 0.907±0.2   | 0.891±0.21  | 0.481±0.08         | <0.001* | <0.001* |
| Mean ADC_{area} (x10^-3mm^2/s)   | 1.125±0.37  | 1.135±0.35  | 0.517±0.08         | <0.001* | <0.001* |

Values are expressed as mean±SD.
*Statistically significance
Obs1:Observer 1; Obs2: Observer 2
lower in lymphoma than the means of RMS (p<0.001 for both observers) and the means of NPC (for ADC\textsubscript{lesion} p=0.004 for obs1; p=0.001 for obs2 and for ADC\textsubscript{area} p=0.003 for obs1; p=0.008 for obs2) (Fig. 4). The mean values of ADC\textsubscript{lesion} (p=0.13 for obs1; p=0.21 for obs2) and ADC\textsubscript{area} (p=0.07 for obs1; p=0.06 for obs2) did not show a significant difference between RMS and NPC.

Inter-observer agreement in ADC measurements was higher for the single slice method (ICC=0.997) than the small sample method (ICC=0.989).

Fig. 2. The MRIs of 6-year-old male patient with RMS (a-c), 12-year-old male patient with lymphoma (d-f) and 13-year-old male patient with nasopharyngeal carcinoma (g-i) with nasopharyngeal and parapharyngeal extension. There is no apparent difference in terms of signal and enhancement characteristics on fat-sat T2WI (a, d, g), and post-contrast fat-sat T1WI (b, e, h). RMS (c) shows higher signal intensity on ADC map compared to lymphoma (f) and nasopharyngeal carcinoma (i).
Discussion

Parameningeal RMS has overlapping findings with lymphoma and NPC in terms of tumor localization and extent. Nasopharyngeal ± parapharyngeal involvement was frequent in both RMS (58.3%) and lymphoma (57.1%) in our study. Further complicating differential diagnosis, previously reported MRI findings of RMS including high T2 signal intensity, prominent enhancement and restricted diffusion are also seen in the other tumors of concern. To our knowledge, there is no previous study comparing MRI characteristics of these three tumors in the literature. In our study, we found a significant difference in terms of ADC values between RMS and lymphoma; in terms of enhancement pattern and presence of necrosis between RMS and lymphoma or NPC. These imaging findings could be used to help distinguish RMS and could guide effective management of these patients.

The age distribution (median age: 4 years) and a slight male predominance in our RMS cohort were compatible with the literature. Although the median age of patients with RMS was significantly smaller than the median age of patients with NPC, there was an overlap between the two cohorts in older ages. The most
common pathologic subtype was embryonic RMS, compatible with the age distribution.

Rhabdomyosarcoma has a locally invasive behavior that is reflected by our high rates of multicompartment involvement (75%) and lack of distant metastasis. Treatment of RMS depends on the histologic subtype, tumor location and stage. It mainly utilizes a multimodality approach that includes systemic chemotherapy and local therapy; consisting of surgery, radiation therapy, or both on a case-by-case basis. Although frequently seen in patients with NPC, skull base involvement was less commonly encountered in RMS (58.3%). In the presence of skull base involvement and intracranial extension, treatment options differ and survival becomes poorer. The intracranial extension was rare in RMS (8.3%) and detected more frequently in patients with NPC, although there was no significant difference between the two groups. Cervical and retropharyngeal lymphadenopathies were significantly more frequent in patients with NPC; distant metastasis was seen in lymphoma. These findings could be used adjunctively with the other imaging findings for tumor discrimination.

The signal homogeneity on T2WI was a common finding (%64.3) in lymphoma compared to RMS and NPC (p=0.006). This finding is compatible with the imaging characteristics of sinonasal lymphoma described previously in literature like the other findings in our lymphoma cohort such as frequent homogeneous enhancement (n=11, 78.6%) and lack of necrosis. T2 signal heterogeneity and heterogeneous enhancement in pediatric RMS due to necrosis or hemorrhage were also reported previously. These two findings were frequently detected in our group of RMS (83.3%) and heterogeneous enhancement was significantly more common than both NPC and lymphoma that could be used as a valuable imaging discriminator to favor the diagnosis of RMS.

Tumor necrosis is characterized by the presence of dead cells with preservation of the tissue architecture. It is reported to be an important hallmark of aggressive tumors and associates with hypoxia and angiogenesis. In our study, neither lymphoma nor NPC showed necrotic parts despite RMS lesions (58.3%). In literature, embryonal RMS was noted to be more homogeneous with a lower rate of necrosis than alveolar and pleomorphic subtypes. Our findings could be attributed due to the size of the embryonal tumors, because almost all (83.3%) presented as large tumors with multicompartment involvement. Additionally, our small-sized cohort has limitations to reflect the general behavior of this histopathologic type.

Diffusion-weighted imaging is efficiently used to differentiate between benign and malignant H&N tumors and helps in avoiding unnecessary invasive diagnostic procedures or surgery. In high-grade malignant neoplasms, ADC values are generally low due to high mitotic activity, increase in cell number and size, decrease in the cytoplasm and extracellular matrix. Several studies particularly performed on adults reported that DWI is useful to distinguish lymphoma from NPC. Our results were compatible; the lymphoma lesions had significantly lower ADC values compared to the NPC and RMS lesions. Since RMS usually presents as a rapidly progressing high-grade tumor, low ADC values could be expected. There are a few studies with a small number of patients that analyzed DWI characteristics of H&N RMSs in literature. The ADC values of RMSs in those studies were reported to range from 0.66x10^{-3} mm^2/s to 0.91x10^{-3} mm^2/s. In the study with the largest number of RMS (n=11) among them, the mean ADC values were found to be 0.78±0.07x10^{-3} mm^2/s. This value is notably lower than the mean ADC values measured by using the single slice ROI method in our RMS cohort (1.125±0.3x10^{-3} mm^2/s for obs1, 1.135±0.35x10^{-3} mm^2/s for obs2) probably due to differences in the methods of measurement. In that study, the ROIs were placed in a single slice avoiding necrotic areas in contrary to our study in which single slice ROIs were drawn in the largest cross-sectional
area of the tumor including necrotic parts. The contribution of necrotic parts with high ADC values is considered to be responsible for higher ADC values in our RMS cohort measured by the single slice ROI method. The mean ADC values measured with the small sample method in our RMS cohort (0.907±0.20x10^-3 mm²/s for obs1 and 0.891±0.21 x10^-3 mm²/s for obs2) are slightly higher than the mean value reported in that study.

In addition to the single slice method, the mean ADC values measured by the small sample method avoiding necrotic parts were also significantly higher in our RMS cohort compared to lymphoma. This probably reflects the histopathologic features of the embryonic type of RMS that was the most common type in our study. Embryonal RMS contains variable cellularity ranging from poorly differentiated primitive mesenchymal cells to highly differentiated muscle cells within a myxoid matrix. The increasing effect of myxoid matrix on ADC in soft tissue tumor was previously reported. Therefore, higher ADC values detected even in the non-necrotic areas of RMS could be explained by the myxoid matrix of the embryonal type.

Although no statistically significant difference was found, the mean ADC values have a tendency to be higher in RMS than NPC in our cohorts. This again probably reflects the presence of necrotic parts commonly found in RMS in contrast to NPC. The small size of our cohorts could be the reason for the difference not being statistically significant between the ADC values of these two tumors. Future studies with larger cohorts are recommended for further evaluation.

Long acquisition time, motion artifacts, and frequent need for general anesthesia are the main difficulties of MRI in pediatric patients. Besides, susceptibility artifacts are commonly encountered in DWI of the H&N region due to excessive air-tissue and tissue-bone interfaces. This may affect the correct localization of ROI and estimation of ADC values. ROI method may also affect the ADC measurements; the small sample ROI method has been reported to yield the worst inter-observer correlation in previous studies concerning thyroid nodules and orbital tumors. Our study supports previous reports; the ADC values measured with the single-slice ROI method showed higher inter-observer correlation than the ones measured with the small sample method. Additionally, the single-slice and whole-volume ROI methods are more representative of the histopathologic characteristics of tumors than the small sample ROI method. This is especially important in the discrimination of tumors like RMS with heterogeneous tissue characteristics due to necrosis/cysts or hemorrhage from more homogenous mimickers.

Although relatively small number of the patients with RMS (n=12) is a limitation, our RMS cohort presents the largest RMS series in the literature. The study has also some limitations due to its retrospective design; the scans were acquired using different scanners with different parameters, which could affect image evaluation. We believe the use of different scanners is not a major limitation. However, possible effect of using different scanners on ADC values cannot be completely excluded and more investigation is needed to make a definite assessment.

The data on which specific gadolinium-based contrast agent was used in the studies could not be found. On the other hand, we believe the use of different contrast agents is not a limitation for qualitative evaluation of enhancement patterns (whether homogenous or heterogeneous).

We also could not perform whole-volume ADC histogram analysis due to the software unavailability. Even though this method has a promising ability to predict histopathologic characteristics of lesions, its application is limited in clinical practice. Another limitation due to the retrospective design was the inability to histopathologically confirm necrotic parts defined in MRIs.
In conclusion, RMS tends to have higher ADC values than lymphoma and has a higher frequency of heterogeneous enhancement and necrotic parts than both lymphoma and NPC. These features could help radiologists to differentiate RMS from the above-mentioned mimickers. Future studies with larger cohorts are recommended to validate these findings.

**Ethical approval**

Institutional Review Board (2020/16-26) approved the study protocol and informed consent was waived by Hacettepe University Institutional Review Board.

**Author contribution**

The authors confirm contribution to the paper as follows: study conception and design: ŞP, EB; data collection: ŞP, EG, EB; analysis and interpretation of results: ŞP, EG, EB; draft manuscript preparation: ŞP, EG, EB. All authors reviewed the results and approved the final version of the manuscript.

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**Conflict of interest**

The authors declare that there is no conflict of interest.

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