

Rhabdomyosarcoma of the genitourinary system in girls — the role of magnetic resonance imaging in diagnosis, treatment monitoring, and follow-up

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ABSTRACT

Objectives: Rhabdomyosarcoma of the genitourinary system in girls is a rare neoplasm, especially in non-dedicated centers. Our work aimed to sum up and present genitourinary rhabdomyosarcomas in girls from the radiological point of view.

Material and methods: We retrospectively reviewed all girls with genitourinary RMS who underwent treatment at the Institute of Mother and Child in Warsaw between 2009 and 2022. We evaluated the demographic, clinical, and pathological patient data and imaging studies.

Results: During the study period, ten patients presented with genitourinary RMS and underwent magnetic resonance imaging (MRI). The median age at the time of diagnosis was 2.8 years, six patients were younger than three years, and four patients were older than ten years. The most common clinical symptoms were tumor fragments protruding from the vagina/falling out of the vagina and vaginal bleeding or discharge, and the most common original location was the vagina. One hundred percent of patients had the embryonal subtype of RMS, and 100% of cases where molecular tests for PAX3/FOXO1 fusion gen status were performed had negative status. At presentation, the median tumor volume was 114 cm³. Eight patients (80%) were classified as clinical group III according to the IRS Group, and most patients (70%) were in a standard-risk group. All patients received multimodal treatment, including surgery and chemotherapy; 60% received radiotherapy. Neoadjuvant chemotherapy was the primary treatment for all our patients. In six patients (60%) with a measurable tumor mass after a biopsy, a gradual tumor volume reduction was observed after induction chemotherapy (approximately ten weeks of treatment) — all of which had a partial response (PR). All our patients (100%) responded completely to treatment.

Conclusions: MRI was performed at every stage of diagnosis and treatment as well as during follow-up. It allowed for staging, monitoring of chemotherapy, and guided surgery.

Keywords: genitourinary system; rhabdomyosarcoma; magnetic resonance imaging (MRI)

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INTRODUCTION

Rhabdomyosarcoma (RMS) represents the most common soft tissue sarcoma in infants and children (50% of pediatric soft tissue sarcomas, 3% of all childhood tumors) and the third most common pediatric solid tumor (after brain tumors and neuroblastoma), accounting for 5% to 15% of all childhood solid tumors. Of these, 15% to 20% arise from the genitourinary tract, with the most common sites of origin being the prostate, bladder, and paratesticular regions, followed by the vagina and uterus [1, 2]. In contrast to the prostate and bladder, the vagina and uterus are favorable sites of rhabdomyosarcoma. Almost

60% of RMS cases are recognized in children younger than six years of age. However, embryonal RMS of the vagina mostly occurs in infants and very young girls, unlike that of the cervix which occurs in older patients [3]. The most common symptoms of urogenital RMS are vaginal bleeding or hematuria, visible introital mass or pathological masses that may protrude from the vagina and undergo autoamputation. Other symptoms include abdominal pain or discomfort in the abdominal or pelvic area, a mass or swelling in the genital area, increased abdominal circumference, urinary or/and stool incontinence, and abdominal pathological mass on palpation. The diagnosis requires, except physical

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Table 1. Intergroup Rhabdomyosarcoma Study group clinical classification system

Group	Definition
I	Localized tumor, completely removed with pathologically clear margins and no regional lymph node involvement
II	Localized tumor, grossly removed with (a) microscopically involved margins, (b) involved grossly resected regional lymph nodes, or (c) both
III	Localized tumor, with gross residual disease after grossly incomplete removal, or biopsy only
IV	Distant metastases present at diagnosis

Table 2. Risk stratification for rhabdomyosarcoma

Risk group	Subgroup	Pathology	IRS group	Site	Node stage	Size & Age
Low	A	Favorable	I	Any	N0	Favorable
	B	Favorable	I	Any	N0	Unfavorable
Standard	C	Favorable	II, III	Favorable	N0	Any
	D	Favorable	II, III	Unfavorable	N0	Favorable
High	E	Favorable	II, III	Unfavorable	N0	Unfavorable
	F	Favorable	II, III	Any	N1	Any
	G	Unfavorable	I, II, III	Any	N0	Any
Very High	H	Unfavorable	II, III	Any	N1	Any

Pathology: *Favorable* = all embryonal, spindle cell, botryoid RMS;
Unfavorable = all alveolar RMS

Site: *Favorable* = orbit, genitourinary non bladder/prostate, non parameningeal head&neck;
Unfavorable = all other sites (parameningeal, extremities, genitourinary bladder/prostate and "other site");

Node stage: *N0* = no clinical and pathological node involvement;
N1 = clinical or pathological node involvement;

Size & Age: *Favorable* = tumor size (maximum dimension) ≤ 5 cm and age < 10 years;
Unfavorable = all others

IRS — Intergroup Rhabdomyosarcoma Study; RMS — rhabdomyosarcoma

examination, imaging studies [ultrasound (US), magnetic resonance imaging (MRI)], and is based on pathological examination of pathological tissue. Treatment for RMS of the vagina and uterus may include surgery to remove the cancerous tissue, chemotherapy, and radiation therapy [4]. The treatment plan depends on the stage and location of the cancer, as well as the child's overall health. The prognosis is generally good with early diagnosis and treatment. However, the individual outcome depends on cancer biology and the child's response to treatment.

We encounter rhabdomyosarcoma quite often at the Institute of Mother and Child in Warsaw, a tertiary referral center for bone and soft tissue sarcomas in children and adolescents, whereas in non-dedicated centers it is an outstandingly rare pathology, especially in genitourinary location, and reported as rare case descriptions [5]. This prompted us to choose this topic.

Objective

The purpose of this study is to sum up and present genitourinary rhabdomyosarcomas in girls from the radiological point of view: diagnostics, treatment decisions and monitoring, and follow-up.

MATERIAL AND METHODS

Our material consists of 10 girls aged between 8 months and 17 years at the time of diagnosis who underwent treatment for RMS of the genitourinary system at the Department of Oncology and Surgical Oncology for Children and Youth in cooperation with the Department of Obstetrics and Gynecology of the Institute of Mother and Child in Warsaw in the years 2009–2022.

We retrospectively evaluated the patients' data and imaging studies. The analysis included age at diagnosis, clinical picture and tumor characteristics — origin, histological subtype, and genetic evaluation. The stage was determined according to the Intergroup Rhabdomyosarcoma Study (IRS) Group clinical classification system which groups patients based on the extent of the tumor, resectability, and microscopic assessment of surgical margins (Tab. 1) [6]. Risk stratification was performed based on the classification mentioned above, other tumor features (site, size, pathology), nodal stage and age at diagnosis (Tab. 2) [7].

Initial tumor volume (at diagnosis), response to treatment, and status at end-of-treatment were reviewed retrospectively based on magnetic resonance imaging (MRI) studies. In each case, a formula for the ellipsoid and round

Table 3. Response evaluation	
Complete response (CR)	Complete disappearance of all visible disease
Very good partial response (VGPR)	≥ 90% reduction of tumor volume or persistence of unclear residuals upon imaging
Partial response (PR > 2/3)	≥ 66% reduction of tumor volume
Minor partial response (PR < 2/3)	< 66% but ≥ 33% reduction of tumor volume
Stable disease (SD)	< 33% reduction of tumor volume
Progressive disease (PD)	≥ 33% increase of tumor volume or appearance of new lesions

tumors was used to calculate tumor volume: $V = a \times b \times c \times 0.52$ in cm^3 . Response to treatment was assessed based on the percentage reduction of tumor volume compared to the initial volume, which then allowed to qualify patients for the appropriate group: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) (Tab. 3) [8].

In addition, regional lymph nodes were evaluated on the initial MRI study — shape, size and presence of hilum were assessed.

In our center, the standard follow-up examinations consist of local assessment on imaging studies (MRI or US) and gynecological examinations — vaginoscopy or hysteroscopy with biopsy of suspicious lesions if needed. Chest X-ray/chest CT (every 3 months) and PET-CT (if applicable) are used to check for distant metastases.

RESULTS

Between 2009 and 2022, ten girls with genitourinary RMS were examined and treated at the Institute of Mother and Child. The median age at the time of diagnosis was 2.8 years, six patients (60%) were younger than three years at diagnosis, and four patients (40%) were older than ten years. The clinical symptoms included: tumor fragments protruding from the vagina/falling out of the vagina (60%) (Fig. 1), vaginal bleeding or discharge (40%), or enlargement of the abdominal circumference (20%). The original locations of the genitourinary RMS were the vagina (40%), cervix (30%), and uterine body (10%); in 2 cases (20%) the origin of the tumor was unclear. All patients had the embryonal subtype of RMS, of which there was botryoid variant in three girls and one spindle cell variant. In 60% of cases, molecular tests for PAX3/FOXO1 fusion gen status were performed; in this group all patients had negative status.

At presentation, the median tumor volume was 114 cm^3 ($5.3\text{--}807.0 \text{ cm}^3$). In two patients there were suspicious regional lymph nodes. No patient had distant metastases at diagnosis, but one developed lung metastases during treatment.

According to the IRS Group, eight patients (80%) were classified as clinical group III. 70% of patients were in a standard-risk group, and 30% were in the high-risk group.

All patients received multimodal treatment, including surgery (Fig. 2) and chemotherapy; 60% received radiotherapy. Neoadjuvant chemotherapy was the primary treatment for all our patients. In six patients (60%) with a measurable tumor mass after a biopsy, a gradual tumor volume reduction was observed after induction chemotherapy (approximately ten weeks of treatment) (Fig. 3) — all of which had a PR. Finally, all our patients (100%) responded completely to treatment and are still in follow-up. One patient (10%) had lung recurrence one year after the first line of chemotherapy and brachytherapy. Still, she finally achieved a complete response after second-line chemotherapy and whole lung radiation.

A summary of patients' data and results of their examinations is shown in Table 4.

DISCUSSION

Although it may seem that the material of a single center collected in this study is not large, when comparing it with large databases one must change one's mind: in the Surveillance, Epidemiology, and End Results (SEER) Program providing information on cancer statistics in the USA, 67 cases of pediatric rhabdomyosarcoma of the female genitourinary tract were identified over the course of 33 years [9]. Knowledge of this neoplasm is essential, not least so that treatment is not delayed by looking for evidence of sexual misconduct, as was the case in one of our patients.

Not all patients came to our institute immediately, hence we do not have imaging studies performed on all of them from the very beginning of the diagnosis, but they were all followed up with US and MRI studies performed at the Department of Diagnostic Imaging of our Institute.

The most common location of RMS of the genitourinary system in girls is vagina [10] and this was confirmed in our material - including the case of an unclear point of origin, but most likely originating in the vagina, half of our patients had vaginal RMS. It is often a pedunculated tumor that protrudes outside the vagina and can undergo autoamputation, as in half of our patients with a clear tumor origin. In such cases, the first diagnosis is based on the clinical picture — visual. Only 0.5% of the RMS of the genitourinary system is located in the cervix, usually in older patients [10] — in our study,



Figure 1. Initial magnetic resonance imaging (MRI) of an 8-month-old girl with vaginal rhabdomyosarcoma (RMS). Visible tumor protruding from the vagina between the labia majora; **A.** STIR, coronal plane; **B.** FSE/T2, axial plane; **C.** FSE/T1, axial plane; **D.** FSE/T1 post-Gd, axial plane

we have three patients with this tumor origin. Two of them at the time of diagnosis were in the second decade of life (one aged 11.1 years, the other aged 17.5 years) and the tumor was an incidental pathological finding after resection of the cervical polyp in these cases. In both above clinical situations, imaging studies are used to search for signs of possible involvement of the reproductive organ beyond the protruding/resected lesion.

In the other, less obvious cases, such as two of our patients, in which enlarged abdominal circumference was the only clinical symptom, imaging methods play a leading role in diagnosis from the beginning. Ultrasonography is usually the first method of imaging soft tissue tumors in children as it is non-invasive, easily accessible, has a high resolution, allows for a quick assessment of tumor size and vascularity, and enables the evaluation of regional lymph nodes. However, imaging is never limited to ultrasound, and MRI is performed which is a method of choice. It allows for precise determination of tumor location, its possible spread

outside the affected organ, its relation to the surrounding structures, and for the assessment of regional lymph nodes and metastases in the examination area (*e.g.*, to the bones).

Computed tomography is not currently used to assess local tumor staging due to too low tissue resolution in relation to needs and therefore the pros and cons tilt decisively to the negative side: too little information in relation to the burden of ionizing radiation and iodine contrast agent. Only chest CT is performed to look for lung metastases in patients with genitourinary RMS.

To complete staging and follow-up in RMS the whole bone examination is mandatory; in our center, positron-emission tomography — computed tomography (PET-CT) is usually performed.

The appearance of RMS on US is non-specific with typically well-defined mass that is inhomogeneous and slightly hypoechoic and can show significant increase of blood flow on Doppler examination. The MRI appearance of RMS is non-specific as well, with intermediate signal intensity

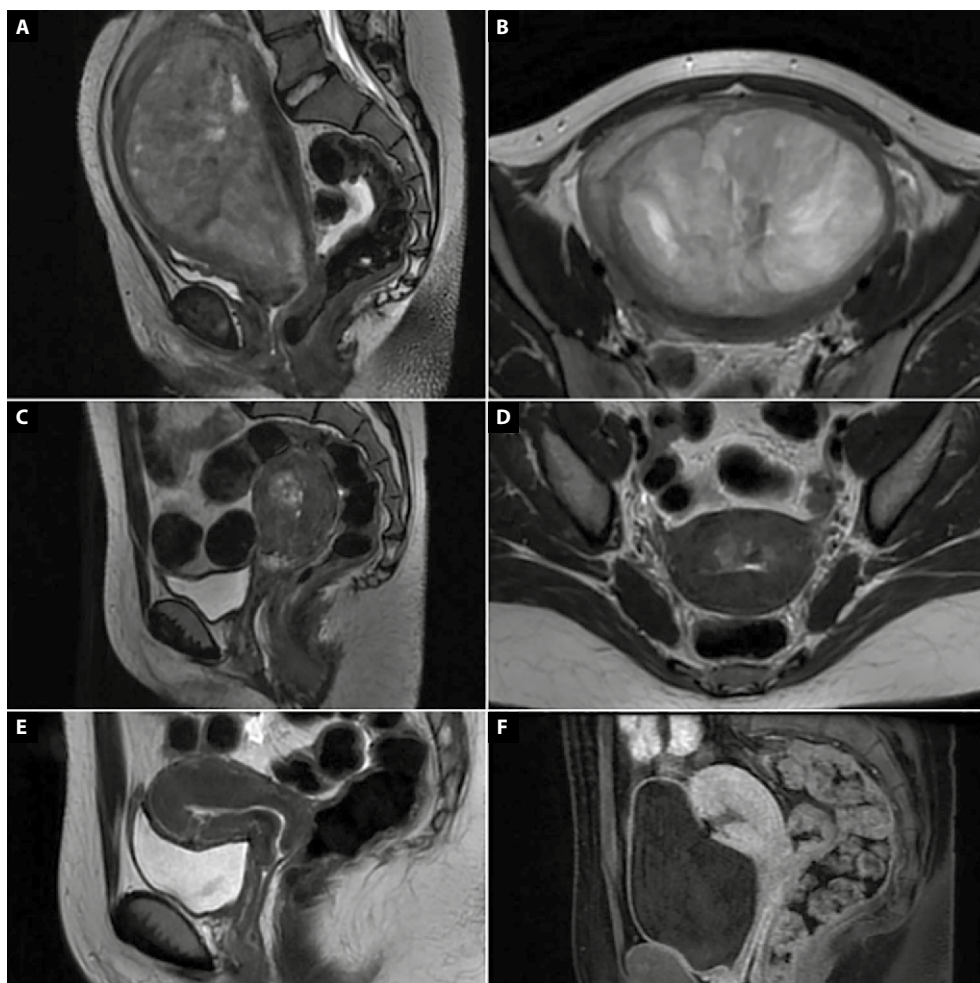


Figure 2. Three magnetic resonance imaging (MRI) studies of a 13-year-old female patient with rhabdomyosarcoma (RMS) of the uterine body. **1.** Initial examination. **A** giant tumor fills the uterine cavity; **A.** CUBE/3D/T2, sagittal plane; **B.** FSE/T2, axial plane; **2.** Examination after the first cycle of chemotherapy (after 14 weeks). Significant reduction in tumor volume; **C.** CUBE/3D/T2, sagittal plane; **D.** FSE/T2, axial plane; **3.** Examination after fertility-sparing resection. Non-enhancing scar and hemosiderin deposits in the anterior/inferior uterine wall; **E.** FSE/T2, sagittal plane; **F.** WATER/T1 post-Gd, sagittal plane

(SI) on T1-weighted images and intermediate to high SI on T2-weighted images, diffusion restriction, and strong contrast enhancement of solid parts (as the tumors may show multicystic architecture). It may also be solid, with a lobulated contour [11].

In our study, all patients (100%) had the embryonal subtype of rhabdomyosarcoma, which accounts for approximately 90% of genitourinary RMS [10] and is associated with a significantly better prognosis than the other subtypes. Genetic evaluation of the tumor for the presence of PAX3/FOXO1 or PAX7/FOXO1 fusions is currently performed to distinguish between subtypes. Eighty percent of the alveolar subtype has a positive status, which means they express the oncogenic genes fusing PAX3 or PAX7 with FOXO1; this expression is not present in any other cancer [12]. In 60% of our patients, genetic tests were performed — all of them had

a negative PAX3/FOXO1 status, which clearly indicates the embryonal subtype. Moreover, localization in non-bladder/non-prostate sites is favorable, like in 80% of our patients (girls with clear tumor origin) [13].

Chemotherapy is the base of multimodal RMS treatment [14]. In 60% of our patients (who had a measurable tumor mass after biopsy), chemotherapy was the main treatment, and in most cases, a partial response to subsequent cycles of systemic therapy was observed, manifested by a reduction in tumor volume on follow-up MR examinations. Local treatment includes surgery and radiotherapy. All our patients underwent surgery at some stage of treatment — at the beginning (in 40%) and, in other cases, to remove residual tumor mass after chemotherapy or recurrence. Postoperative chemotherapy was mandatory and received by all our patients. Radiotherapy was realized as teleradiotherapy or

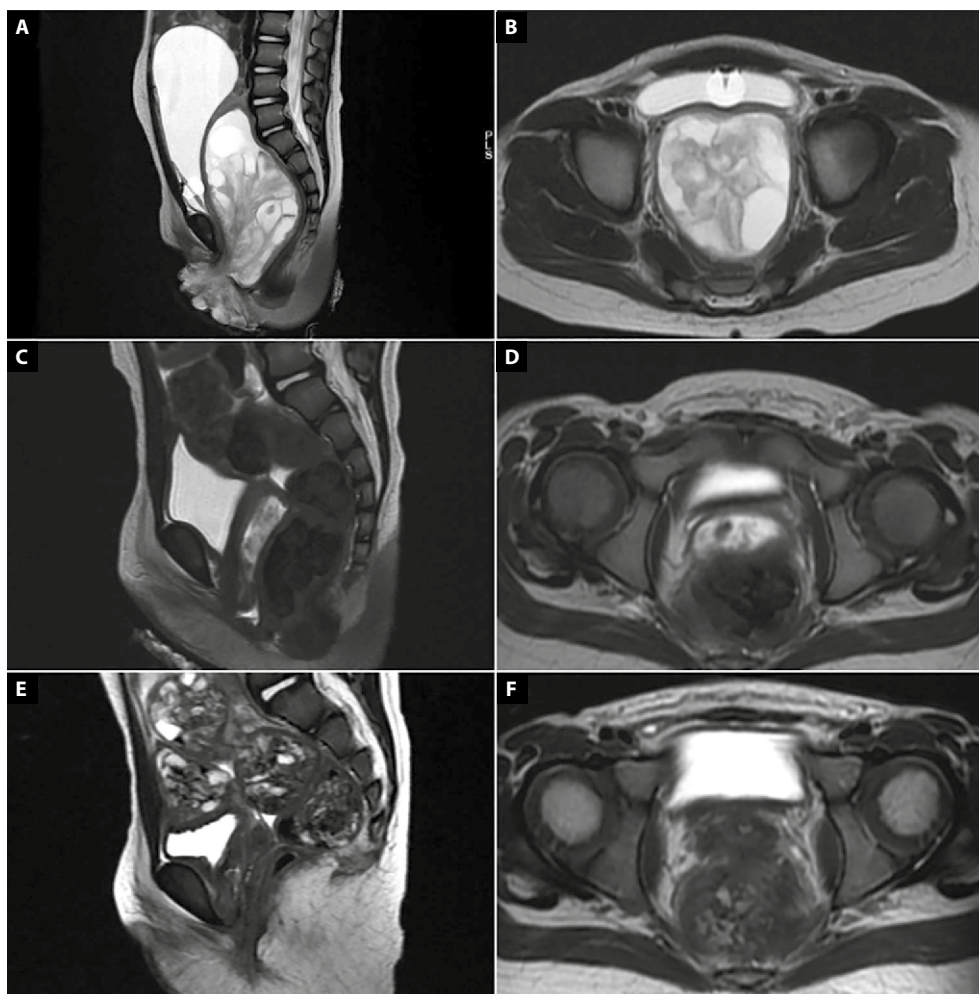


Figure 3. Three consecutive magnetic resonance imaging (MRI) studies of a 2-year-old patient with vaginal rhabdomyosarcoma (RMS) show a very good response to chemotherapy; **1.** Initial study. A large tumor fills the vagina and protrudes outwards; **A.** FSE/T2, sagittal plane; **B.** FSE/T2, axial plane; **2.** Examination after ten weeks of chemotherapy. Reduction of tumor volume, no protruding part; **C.** FSE/T2, sagittal plane; **D.** FSE/T2, axial plane; **3.** Follow-up examination after 20 weeks of chemotherapy. There is no visible tumor in the vagina **E.** FSE/T2, sagittal plane, **F.** FSE/T2, axial plane

brachytherapy. Postoperative radiotherapy was performed in 6 girls (60%) and in 3 cases it was brachytherapy.

Magnetic resonance imaging is a modality of choice to show the potential residual mass and to plan the fertility-sparing resection which is an issue of utmost importance in girls and requires close radiological-gynecological cooperation. In one case of uterine body sarcoma, which almost reached the diaphragm before chemotherapy, the first step after oncological treatment was an operative hysteroscopy. The main goal was to detect any neoplastic tissue in the anterior uterine wall. Hysteroscopy was performed in the operative room under general anesthesia with a 10 mm resectoscope (Gynecare Hysteroscope, Johnson and Johnson, New Jersey) with bipolar energy. The samples were taken from the anterior wall from a place that was identified on MRI as a possible residual sarcoma. Pathomorphological samples revealed no neoplasia. As hysteroscopy can only

remove tissue from the uterine cavity and from the cavity side of the uterus wall, the next step was to perform laparoscopy to remove all other uterine tissue that was identified as suspicious on MRI, from the anterior uterine wall. The surgery was performed in patient in a 30° Trendelenburg position under general anesthesia, using a carbon dioxide insufflation laparoscopy system (Karl Storz, Munich, Germany). The intra-peritoneal laparoscopic view was obtained *via pneumoperitoneum*, and laparoscopic instruments were introduced through the abdominal wall *via* 0.5–1-cm valveless trocars. Both monopolar cautery and scissors were used, and a suspicious part of the front uterine wall was removed. The uterus cavity was exposed. Then, the anterior wall was closed with intracorporeal absorbable sutures. Because the patient was qualified — according to the oncological protocol — for the small pelvis radiotherapy in the next step of treatment, during the same operation transposition of the

Table 4. Patients' data and results of their examinations

No.	Age at diagnosis (years + months)	Clinical picture	Localization	Pathology subtype and variant	Genetics (PAX3/FOXO1 fusion status)	Initial volume [cm ³]	Suspicious regional lymph nodes	Distant metastases	IRS group	Risk stratification	Treatment	Response	Time of observation (years + months)
1	17 + 6	Vaginal bleeding	Cervical polyp	Embryonal, variant unknown	Negative	Initial study not available	No	Yes	III	SRC	Surgical, cht, rx	CR	2 + 0
2	1 + 0	Vaginal bleeding + tumor protruding from the vagina	Vagina	Embryonal, botryoid	Negative	81	No	No	III	SRC	Cht, surgical	CR	2 + 6
3	11 + 1	Vaginal bleeding	Cervical polyp	Embryonal, spindle cell	Negative	Initial study not available	No	No	I	SR B/C	Surgical, cht	CR	2 + 6
4	13 + 5	Abdominal circumference enlargement (mass in the lower abdomen)	Uterine body	Embryonal, variant unknown	Negative	807	Yes	No	III	HR F/H	Cht, surgical, rx	CR	2 + 3
5	0 + 8	Tumor protruding from the vagina	Vagina	Embryonal, variant unknown	Data not available	5.3	No	No	II	SRC	Surgical, cht, rx	CR	7 + 8
6	2 + 9	Vaginal discharge + masses falling out of the vagina	Cervix	Embryonal, variant unknown	Negative	6.7	Yes	No	III	HRE	Cht, surgical	CR	3 + 0
7	17 + 3	Menstrual disturbance + tumor protruding from the vagina	Vagina	Embryonal, botryoid	Data not available	582	No	No	III	SRC	Cht, surgical, rx	CR	3 + 6
8	1 + 7	Data not available	Unclear origin — vagina?	Data not available	Data not available	Initial study not available	Data not available	No	data not available	data not available	Cht, surgical, rx	CR	13 + 6
9	2 + 3	Tumor protruding from the vagina	Vagina	Embryonal, botryoid	Data not available	147	No	No	III	SRC	Cht, surgical	no end-of-treatment examination	0 + 5
10	2 + 10	Data not available	Unclear origin	Rhabdomyofibrosarcoma infantile	Negative	Initial study not available	Data not available	No	II/III	HR E/F	Surgical, cht, rx	CR	3 + 4

IRS — Intergroup Rhabdomyosarcoma Study; SR — standard risk group; HR — high risk group; B/C, F/H, E/F — subgroups; Cht — chemotherapy; Rx — radiotherapy; CR — complete response

ovaries outside the pelvis and outside the potential radiotherapy field was performed. During this part of the procedure the ovaries were mobilized and grasped. The ureters were identified through the peritoneum. The utero-ovarian ligament was cauterized and severed using bipolar forceps for coagulation and scissors alternatively. The fallopian tubes were separated from the ovaries through the mesovarium. The peritoneum then was incised along the infundibulopelvic ligament to mobilize the ovaries completely. Dissection of the ovarian vessels was performed up to the level of the aortic bifurcation. The ovaries were transposed laterally to the paracolic gutters and fixed securely with use of two sutures. Two metal clips were applied to each transposed ovary to guide subsequent roentgenographic localization. Pathomorphological samples revealed no neoplasia.

As in case of adnexal masses that have indeterminate appearance on US, MRI is a modality of choice in the diagnosis of unclear pathological masses in the transposed ovaries which – depending on the site of transposition — may be difficult to reach with US.

Only two patients (20%) had a local relapse during treatment, diagnosed on follow-up MRI. One of these patients had unfavorable prognostic factors, such as age > 10 years and initial maximum tumor dimension > 5 cm. Magnetic resonance imaging examinations at the end of treatment showed no abnormalities or only scars and hemosiderin deposits after surgical procedures were visible.

CONCLUSIONS

In conclusion, magnetic resonance imaging was performed at every stage of diagnosis and treatment of our patients as well as during follow-up. It allowed for staging, monitoring of chemotherapy, and guided surgery.

Article information and declarations

Data availability statement

Additional data is available from the corresponding author on a reasonable request.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki. Written informed consent for clinical imaging was obtained from the patients/patients' guardians.

Author contributions

PS collected and analyzed the imaging data, analyzed the literature, and wrote the text; ZM and AR completed the oncological part of the text; TI completed the gynecological

part of the text; MBF conceptualized and supervised the study, reviewed the text. All authors read and approved the final manuscript.

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None.

Conflict of interest

All authors declare no conflict of interest.

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