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DOCTORAL THESIS

**CONTRIBUTIONS TO THE DIAGNOSTICS OF OVARIAN AND
TESTICULAR, GONADAL AND PARAGONAL TUMORS IN
CHILDREN**

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I.STUDY 1: A 10-YEAR RETROSPECTIVE STUDY OF THE RISKS AND PECULIARITIES IN PEDIATRIC PATIENTS WITH (PARA)GONADAL TUMORS AND CYST.

CONTEXT

Pediatric testicular and ovarian tumors are rare, having an incidence rate of 0.3-12:100000 and 2.6-10.7:100000, peaking below age one (18:1000000) and at 15-19 (28:1000000) and although curable with favorable diagnoses, this is possible when discovered early. Gonadal tumors have vague presentation with multi-ethiology and this makes it difficult to suspect or detect them for sure until they reach a late stage, as observed at 70% among women with ovarian tumors from studies, which leads to an unfavorable prognosis, such as death or infertility. Studies showed the daily cost of hospitalization of pediatric cancer patients is 70% higher than for other diseases, and they stay an average of eight days more; also, delayed diagnoses increase patients' costs. Gonadal and germ cell tumors amongst other pediatric tumors in Romania was 5% for 0-19 years, 3.4% for 0-14 years and 12.2% for 15-19 years. The pediatric cancer patients' survival in Romania was 72% (2010 -2017) for 0-19 years, which is below the media of European countries (81%); also, the survival rate in the pediatric patients with gonadal and germ cell tumor dropped from 85%, to 81% in 2014-2017, and a 6% increase was observed in ages 0-14. Also, a 25% increase in malignant tumors incidence is predicted by 2025. The incidence rate of gonadal tumors in Europe is 12%,10.7%. World Health Organization reported that awareness, early tumors detection, and appropriate treatment, varied significantly between Western and Eastern European countries, leading to a 9%-57% mortality rate. The purpose of this study is to evaluate the epidemiological population of pediatric patients affected by gonadal tumors in the west and east of Romania, to analyze the risk to which they were exposed, and the specific clinical features presented by children with gonadal tumor, in order to detect gonadal tumor, easily and quickly identifying efficiently malignancy, the tumor type, stage, ability to predict metastases and recurrence and the prognostic of the patient, for better patient management and favorable prognosis, avoiding high risk factors to prevent or reduce malignant gonadal tumors

SUMMARY OF FINDINGS

The presentation of patients having malignant and non malignant tumors observed in our study population is presented in Table 1. Other symptoms not listed or not present were not observed in the two groups to make a comparison or were present in less than five patients. Of the 210 patients in our study, 98 patients had malignant tumors, and 112 patients had benign tumors (Figure 1) 36% of the patients at puberty had malignant tumors, and the number of patients per year in 2010-2010 is reported; also, 52.4% of the female had malignant tumors, with a ratio of 1:1.45 male/female.

From patients in our study with different types of pain, those with dull pains had the highest numbers (71), and from these, 47(66%) patients had malignant tumors, while 24(34%) had benign tumors 39/98(40%) patients had grade 1 tumors and 45/98(46%) patients presented at stage II (Figure 14) and 34 (16.2%) patients had metastasis.

20/26 patients with viruses (human herpesvirus 1-6, rubella hepatitis, human immunodeficiency virus, and tuberculosis) had malignant tumors, 35.2% of patients with malignant tumors had leukocytosis, while 64.8% of benign patients had leukocytosis. Two boys brought from accidents were found accidentally with malignant tumors, having an asymptomatic presentation. 45% of the 35 patients with appendicitis were operated on for gonadal tumors, and appendicitis was discovered, but in 54%, it was during appendectomy that we discovered the tumor growth.

In this study, we saw a case of repeated torsion that was a sign of a tumor in a patient and another case in which the patient experienced bleeding, irregular menstruation, early puberty, accompanied by abdominal pain, and with the help of inhibin B, AMH, the FISH test of Tp53 it was indicated earlier as juvenile ovarian granulosa cells that require further investigation and treatment, before we performed radiological, exploratory (laparoscopy) and histopathological examination to confirm and the previous examination helped us to establish the best choice of management of the patient, preventing relapse.

Additionally, the tissue found in the MTs in our study were nervous tissues (65%), squamous epithelium (80%), adipose tissue (70%), muscle mesoderm (81%) bone (69%), teeth (50%), and cartilage (75%) and intestinal epithelium endoderm (88%) acini sero-mucinoses (60%), and respiratory (96%).

Amongst patients with malignant and benign, MGCTs and ITs had the highest prepuberty-aged children 9(22%) and MGCTs amongst children at puberty 17(30%). 17(43%) males had MGCTs, and 14(24%) females had ITs; 10(24%) children with tumor sizes ≥ 10 cm, 2(50%) patients who died, had gonadectomy 26(29%), bleeding 6(32%), virus 6(30%), elevated tumor markers 26(33%), GCTs 26(36%), loss of appetite 12(30%) and weight 10(36%) all had MGCTs. ITs have the highest number of patients with Abdominal distention 9(23%), and leukocytosis 5(26%) patients. The majority of patients in each stage were ITs 6(30%) and 14(31%) for stages 1 and II, while MGCTs 6(29%) and 6(50%) for stages III and IV, while for tumor grade I, II, III, ITs 16(41%), MGCTs 9(32%), 12(41%) and MGCTs and dysgerminoma 1(50%) for grade IV. The highest tumor types for multilocular cyst+solid 9(31%), and solid 12(36%) was MGCTs and for multilocular solid 13(45%) was ITs, rhabdomyosarcoma had the highest patients with Non-GCTs 14(54%) and tumor size < 5 cm 2(20%).

Analyzing the Relative Risk, the chances of getting malignant tumors increase with each unit of the statistically significant risk factors; obesity-1.34, breastfeeding ≤ 5 months-1.11, stress-1.33, hormone-1.16, smoking-1.36, positive heredo-genetic history-1.10, abnormal birth weight-1.08, rural residence area-1.00, Pollution-1.30, menstruation disorders- 1.15, and malformations-1.65 times respectively. Urinary tract infection was slightly significant 1.28 (0.053), and rhesus positive was significant only at the univariate analysis 1.61(0.037). Analyzing the highest Coefficient estimate (β) of the risk factors using multinomial logistic regression amongst malignant tumors patients with MGCT patients as the dependent variable revealed; stress GrCTs (2.13), Rhesus Positive ITs (2.97), Pollution ITs(1.80), and menstruation disorders GrCTs (2.73), while for multivariate analysis stress- GrCTs (2.10), pollution- ITs(1.75), rhesus positive ITs(3.41), and menstruation disorders GrCTs (2.80) was observed. 102/210(48.6%) children had congenital malformation, 77(75%) had malignant tumor. The patients in total and

patients with malignancy who presented with genetically related malformations was 28 (27%) and 21(75%), unlike non-genetic malformations 87(85%) and 67(77%); also, they were mainly facial, 39(45%) and 29(74%), especially eye malformations 28(32%), 18(64%). In genetic-related malformations, in total, DSD had the most patients 17 (61%), but amongst patients with malignant tumors 10 Patients had DSD and 10 patients had Down syndrome.

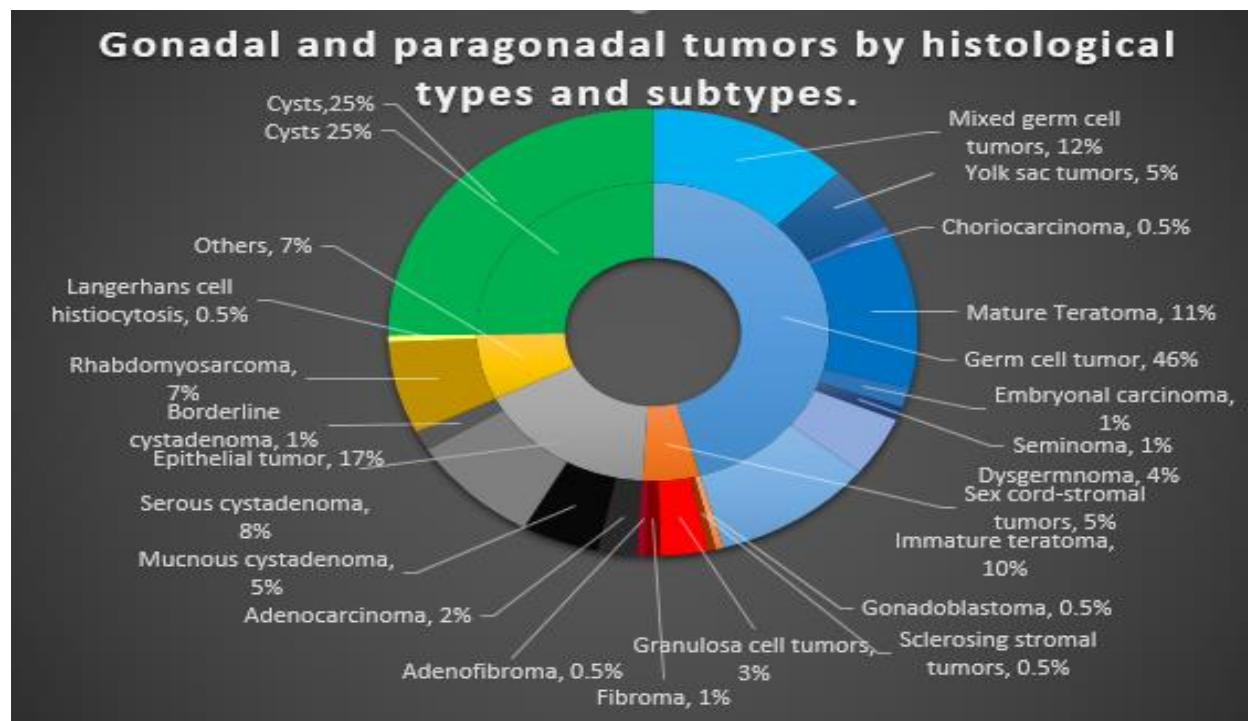


Figure 1. Histological classification of the tumors in this study population

Peculiarities	N(%)	Malignant tumors N(%)	Bening tumors N(%)	P-value
Tumor types	210	Total - 98 Immature Teratoma- 21(10%) Rhabdomyosarcoma- 14(6.7%) Dysgerminoma- 9(4.3%) Mixed germ cell tumor- 26(12.4%) Seminoma- 2(1%) Adenocarcinoma- 5(2.4%) Langerhans cell histiocytosis- 1(0.5%) Embryonal carcinoma- 3(1.4%) Granulosa cell tumor- 6(2.9%) Choriocarcinoma- 1(0.5%) Yolk sac tumors- 10(4.8%)	Total - 112 Gonadoblastoma- 1(0.5%) Sclerosing stromal tumor- 1(0.5%) Mature Teratoma- 24(11.4%) Fibroma- 2(1%) Adenofibroma- 1(5%) Mucinous cystadenoma- 10(4.8%) Serous cystadenoma- 17(8.1%) Borderline cystadenoma- 3(1.4%) Cysts- 53(25%)	
Age:Pre-puberty (0-9)	56	41 (73%)	15 (27%)	0.001
Puberty (10-17)	154	57 (37%)	97 (63%)	

Sex:Male	47	40 (85%)	7(15%)	0.001
Female	163	58 (36%)	105(64%)	
Size:<5	37	10 (27%)	27(73%)	0.001
5-10	110	47 (43%)	63(57%)	
>10	63	41(65%)	22(35%)	
Tumor location - Right	79	32 (41%)	47(49%)	0.373
Left	110	55 (50%)	55(50%)	
Bilateral	21	11 (52%)	10(48%)	
Pain location - Right	61	30 (49%)	31(51%)	0.932
Left	104	48 (49%)	56(51%)	
Both side	38	18 (47%)	20(53%)	
Pain Radiates to leg	53	26 (49%)	27(51%)	0.687
Repetition	20	13 (65%)	7(35%)	0.084
Death	4	4 (100%)	0(0%)	0.031
Diagnosed prenatal	8	2 (25%)	6(75%)	0.210
Gonadectomy	116	89 (77%)	27(23%)	0.001
Asymptomatic	7	2 (29%)	5(71%)	0.329
Appendicitis	35	16 (46%)	19(54%)	0.901
Loss of appetite	59	40 (68%)	19(32%)	0.001
Loss of weight	33	28 (85%)	5(15%)	0.001
Leucocytosis	54	19 (35%)	35(65%)	0.050
Fever	16	5 (31%)	11(69%)	0.191
Constipation	21	13 (62%)	8(38%)	0.140
Vomit	9	2 (22%)	7(78%)	0.329
Bleeding	26	19 (73%)	7(27%)	0.001
Abdominal distention	63	39 (62%)	24(38%)	0.004
Ascitis	14	10 (71%)	4(29%)	0.055
Germ cell tumors	97	72 (74%)	25(26%)	0.001
Not Germ cell tumors	113	26 (23%)	87(77%)	
Loculation:Unilocular cyst	39	0 (0%)	39(100%)	0.001
Unilocular cyst+solid	22	2 (9%)	20(91%)	
Multilocular cyst	33	5 (15%)	28(85%)	
Multilocular cyst+solid	50	29 (58%)	21(42%)	
Multilocular solid	33	29 (88%)	4(12%)	
Solid	33	33 (100%)	0(0%)	
Compressed organs	36	20 (56%)	16(44%)	0.240
Elevated tumor markers	88	80 (91%)	8(9%)	0.001
Viruses	26	20 (77%)	6(23%)	0.001
Time of Symptoms: 1-2 days	102	38(37%)	64(63%)	0.001
3-6 days	83	48(58%)	35(42%)	
≥7 days	28	20(71%)	8(29%)	

Table 1. The peculiarities observed in our study population, for patients with benign and malignant tumors.

CONCLUSION

Exposure to pollution, (especially in mines and exposure to agricultural chemicals fertilizers), obesity, malformations (especially non-genetic malformations, and eye malformations), smoking, and stress, are the strong risk factors and top five among other risks that cause gonadal malignant tumors in children, especially GrCTs, Dysgerminoma, STs, and GrCTs, with MGCTs being dependent variable. Menstrual disorder and breastfeeding <5 months can lead to malignant and non-malignant gonadal tumors. Avoiding these risk factors will prevent and reduce pediatric gonadal tumors. Medical investigations are essential for those who present malignant tumor peculiarities, including weight loss, increased tumor markers, solid (multilocular) mass at the radiological examination, bleeding and viruses, sugar intake >65g/day because

they have >70% chance of having malignant gonadal tumors, especially if they are exposed to the above risk factors. This will allow us to identify early on if there is any malignant tumor, especially MGCTs, ITS, and dysgerminoma, and to achieve successful patient management, which leads to a favorable prognosis with minimal side effects.

II. STUDY 2: A 10-YEAR RETROSPECTIVE SINGLE-CENTER STUDY OF ALPHA-FETOPROTEIN AND BETA-HUMAN CHORIONIC GONADOTROPIN IN ROMANIAN CHILDREN WITH (PARA)GONADAL TUMORS AND CYSTS

CONTEXT

The national vital statistics report, 2019, shows that 51% of children's deaths per year were caused by cancer, outpacing the combination of deaths from all other diseases in children. Study 2 analyzes the results of tumor markers, which were analyzed as a predictor of malignant tumors. In Europe, amongst children (>1-year), malignant tumor is a top-ranking cause mortality rating 1–4 deaths/100,000 and germ cell tumours (GCTs) and gonadal tumours in fourth place (6%) according to the Surveillance, Epidemiology and Final Results (SEER) programme (seer.cancer.gov).

Gonadal germ cell tumors (GCT) are rare in children, and the common tumor markers used to detect and monitor gonadal GCT are beta-human chorionic gonadotropin (β -hCG) hormones and the antigen alpha-fetoprotein (AFP). AFP is a glycoprotein derived from the fetus yolk sac and liver that is elevated in newborns but decreases at 8 months, when children have values similar to adults. The peptide β -hCG is produced by trophoblasts; hence, β -hCG is highly elevated in trophoblastic tumors, including gestational and nongestational choriocarcinoma (CC) rarely seen in females but a frequent component of nonseminomatous testicular GCT in males. Hence, β -hCG is one of the obligatory tumor markers required in the differential diagnosis of testicular tumors. The discovery of the appropriate tumor marker for the detection and management of patients with gonadal tumors is essential. The aim of this study is to identify the predictive ability of AFP and the tumor marker HCG diagnostic tools to help detect solidly the diagnosis of malignant gonadal tumor, definitively, easily and quickly in diagnosis, effectively identifying malignancy, tumor types to detect, the tumor stage, and whether we can use it to predict the progression of the tumor metastases, the response to treatment and recurrence in children with gonadal tumor

SUMMARY OF FINDINGS

From 86 patients with malignant tumors, 55.8% patients had elevated AFP/ β -hCG. AFP was elevated in 52.3% patients, and β -hCG was elevated in 25.6% patients, with β -Hcg only, elevated in only three patients, only AFP in 26 patients, and AFP + β -hCG in 19 patients.. The

sensitivity, specificity, and ROC values in malignant GCT was AFP + β -hCG- 0.828, 67.2%, 100%; AFP- 0.813, 64.1%, 100%; β -hCG- 0.664, 32.8%, 100%. This ranks their diagnostic ability from AFP + β -hCG and AFP to β -hCG. Most patients with elevated AFP/ β -hCG had mixed GCT (25/48) (Figure 2) and all patients with YST or its componenets (62%) had elevated AFP unlike those without YST (37.5%) (P value <0.001). 17/19 patients with elevated AFP + β -hCG had mixed GCT

All 48 patients with elevated AFP and β -hCG had malignant tumors. Unelevated markers and favorable prognoses was observed in patients with cyst and non-GCT. In GCT patients, 4/35 (11.4%) with unelevated AFP/ β -hCG had poor prognosis rate, which increased in patients with elevated AFP/ β -hCG- 24/43 (55.8%) and elevated AFP + β -hCG 15/19 (78.9%), 11 of the 15 (73.3%) patients were at pubertal age. 76.5% of patients with metastasis, had elevated AFP or β -hCG; and 44% of patients had elevated AFP + β -hCG, Among patients with malignancy, 4/22 (18.2%) patients with non-GCT had metastasis compared to 30/64 (46.9%) patients with GCT- 60% having mixed GCT, p-value 0.018. Most patients had no recurrence, indifferent to AFP/ β -hCG elevation. Only four non-GCT patients having MC, RMS, AC, and GrCT (adult + juvenile type), with unelevated markers had recurrences and for GCT, an IT patient with unelevated markers and three patients with elevated markers, having YST and mixed GCT, had recurrences. The only patient with tumor recurrence who had elevated AFP + β -hCG and metastasis, diagnosed with mixed GCT, died.

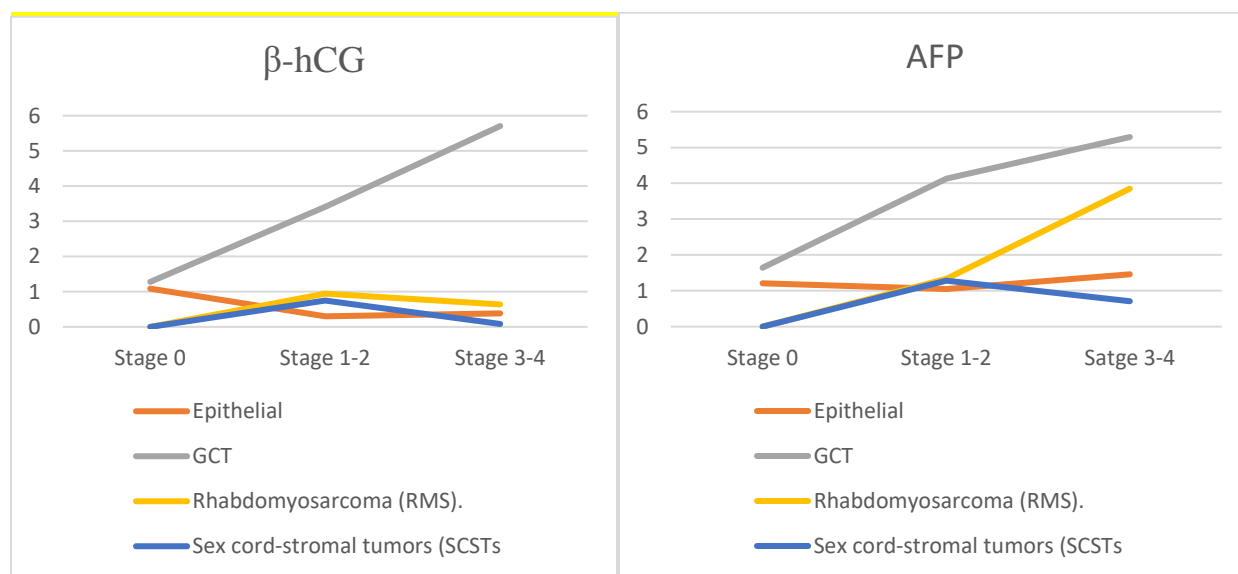


Figure 2: The distribution of β -hCG and AFP marker values in all tumor stages.

The characteristic operating curve of the receiver (ROC) of AFP, HCG and AFP+HCG in all patients show in Figure 21. Area under the curve (AUC) was: AFP+HCG 0.767 (SE 0,041, 95% CI: 0,690-0,845), AFP - 0,756 (SE 0,040, 95% CI 0,677-0,835), HCG -

0,622 (SE 0,048, 95% CI 0,529-0,716) and with p-value 0,0001, 0,0001, and 0,019, classifying the detective capability from β -hCG, AFP and then β -hCG+AFP (Figure 3)

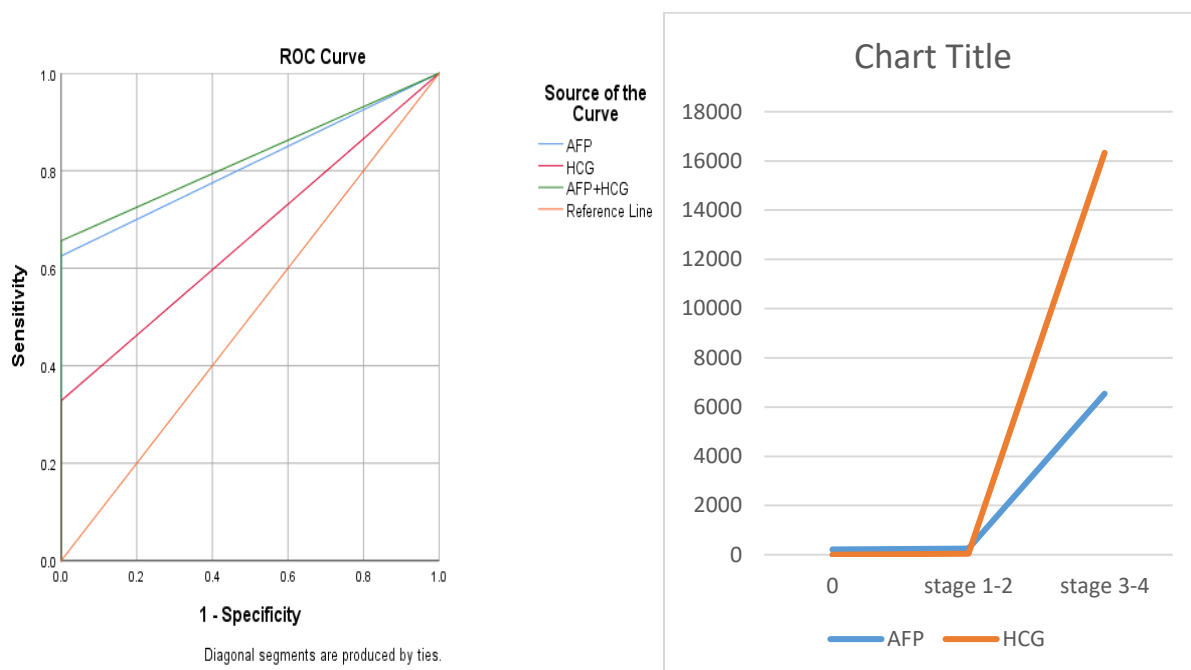


Figure 3. AFP and HCG tumor marker. A) The characteristic curve of operation of the receiver (ROC) of AFP (Alpha-fetoprotein), (HCG (Human chorionic beta-gonadotropin) and AFP+hCG (Alpha-fetoprotein and beta-human chorionic gonadotropin) in all patients with GCT. B) A graph showing the distribution of AFP and HCG marker values across all tumour stages.

CONCLUSION

AFP/ β -hCG could primarily detect malignant GCT and determine tumor type and prognosis in Romanian children. Patients with GCT having markedly elevated AFP + β -hCG levels suggest a poor prognosis, especially if it is elevated post-chemotherapy in the presence of recurrence or metastasis and at pubertal age. AFP effectively differentiates malignant from nonmalignant tumors. β -hCG is useful in detecting malignant tumors not secreting AFP. However, using both tumor markers is better, especially in identifying mixed GCT. Combining other tumor markers such as miR-371a-3p, will increase the ability to identify other tumor types that do not cause AFP/ β -hCG elevation. Additionally, unlike metastasis, recurrence is unrelated to AFP/ β -hCG elevation, and in mixed GCT, the components and quantity of tumors present determine AFP/ β -hCG values.

III.STUDY 3: A 10-YEAR STUDY OF CHILDREN WITH GONADAL TUMORS AND DISORDERS OF SEX DIFFERENTIATION, IN ROMANIA.

CONTEXT

Gonadal tumors arising from the testis or ovary, rarely found in children, has an incidence rates of 2.6:100000 and 1-12:100000 respectively, with a higher chance of cure although complicated, when discovered early. Disorders of sex development (DSD) are also rare, complicated, and delicate conditions where different phenotypic sex anatomical structures, gonadal, or genetic chromosomal are atypically found in the same individual, having an incidence rate of 1:5,000 live births. Studies revealed an increased risk of gonadal malignancy in children is associated with congenital malformation (non-chromosomal or chromosomal related, including genital organ abnormality related to DSD), and the risk increases with the number of malformations, in children more than adults. There are risks of malignancy in people with DSD if; during Embryogenesis immature germ cells persist, also in the presence of histological dysgenetic gonad development, gonadoblastoma (+Y), intrabdominal location of the gonads, OCT3/4 (+) marker, nonscrotal partial androgen insensitivity syndrome (PAIS), Frasier, Denys-Drash (+Y), Intermediate Turner (+Y), 12th and 9th chromosome gain, aneuploidy, loss of 6q and elevated tumor markers. Prophylactic gonadectomy is one of the treatment management for children with DSD, with a high risk of developing malignant gonadal tumors.

Amongst patients with ovarian și testicular tumor some comorbidities was observed that may serve as predictors or even risk factors of malignant tumors. In our study of comorbidities, we analysed more malformations, because it was a remarkable comorbidity among our pediatric patients with testicular and ovarian tumors and yet it was diverse. Many were non-genetic malformations than genetic related malformations, and the frequency of malformations is in patients with malignant tumors (77 patients), than patients with benign tumors (25 patients). Facial malformations with a total of 39 patients were mainly observed in patients with non-genetic malformations, especially those with eye malformations (28 patients). Among patients with genetic malformations, patients with problems of sexual development were mostly observed (17 patients). We aim to investigate the presentation of DSD children having malignant gonadal tumors, in order to use it to predict malignancy.

SUMMARY OF FINDINGS

In this study, from 210 children with gonadal tumors we identified 17 (8.1%) children with Disorders of sex development (DSD). Ten children had malignant tumors, while seven children had non-malignant tumors, cystadenoma (71.4%) was majorly noted. 8/17 children had gonadal tumors presentations, on examination, DSD was identified, from which 75% were children with malignant tumors. Conversely, nine children that presented with DSD complaints, were later diagnosed with gonadal tumors.

Obesity was observed in 3/7 children (42.9%) with non-malignancy, unlike 9/10 children (90%) with malignancy p-value 0.036. Tumor markers was elevated in AFP (Immature teratoma, yolk sac tumor, mixed GCT), B-HCG (seminoma, mixed GCT), LDH (seminoma, mixed GCT, two

immature teratomas, yolk sac tumor, two dysgerminomas), and Ca-125 (Dysgerminoma, immature teratoma) were elevated in 70% of children (7/10) with malignancy and 14.3% of children (1/7) without malignant tumors (borderline cystadenoma-LDH, Ca-125) P-value 0.023. We observed OCT 3/4 markers was used in few children (five cases- 29%), as immunohistochemistry was performed to confirm malignancy. Three children with seminoma and two dysgerminoma had positive findings, while immunohistochemistry was negative in two children with yolk sac tumors and mixed GCT.

Malformations in other systems were observed in 9/10 children (90%) with malignancy in contrast to 2/7 children (28.6%) without malignancy p-value 0.001 (Table 2). Psychosocial issues were observed in four children (57%) and absent in three children (43%) with non-malignant tumors ages ≤12 years, and absent in five children having malignancy, with 4/5 (80%) of ages ≤10 years. In total, psychosocial issues were observed in 9/10 children (90%) >12 years, compared to 0/7 children (0%) ≤12 years, P-value 0.001. Gonadectomy in agreement with the choice of the children's family, was performed in two non-malignant tumor children (22%), compared to all children (100%) with malignancy P-value 0.001. From the 17 children with DSD, the sensitivity in identifying testicular tissues for total testosterone, and AMH was 72.7%, and 63.3%, while the specificity was 83.3% and 80%.

S / N	DSD Diagnoses	Sex	Age	Benign Tumor	Tumor Stage	Elevated tumor marker	Malformation	obesity	Gonadectomy	Psychosocial issues	Presentation	Gonadal tissue	Total Testosterone (ng/ml)	LH (UL/L)	FSH (UL/L)	Estradiol (pg/ml)	AMH (ng/ml)
1	Turners Syndrome (45X/46XY Mixed MGD)	F	13	Gonadoblastoma	No	No	Short, short neck and delay hands bone age	Yes	No	Yes	Short	Ovary	**0.33(0.26-1.17)	**12.6(<0.09-14.3)	**68.2(0.05-7.92)	**<10(10-117.44)	n.a
2	Klinefelter (XXY)	M	15	Seros cyst - adenoma	No	No	No	No	yes	yes	Micropenis cryptorchidism ,Gynecomastia	Testis	0.9(1-12)	24(0.8-8.7)	30(0.6-6.9)	40.5(≤38)	0.36(<13)
3	PAIS (46XY)	F	10	Mucinos cytsadenoma	No	No	No	yes	No	No	Ambiguous genitalia	Testis	1(<0.07-0.44)	15(<0.02-4.8)	2(0.5-6.0)	*7.2(≤24)	350(0.36-5.9)
4	PAIS (46XY)	F	13	Papillary Seros cystadenoma	No	No	Nasal septal deviation	No	No	yes	Amenorrhea	Testis	4.4(<0.07-0.75)	25.5(<0.02-11.7)	2.26(0.9-8.9)	6(15-85)	427(0.49-6.9)
5	Klinefelter (XXY)	M	12	cyst	No	No	No	yes	No	No	Micropenis cryptorchidism	Testis	0.08((<0.07-8)	12(0.1-5.7)	15(0.6-6.9)	19(≤16)	1.1(<13)
6	CAIS (46XY)	F	11	Mucinos Borderline cystadenoma	No	Yes	No	No	yes	No	Abdominal pain	Testis	2(<0.07-0.44)	48(<0.02-11.7)	6(0.9-8.9)	*9.7(≤60)	201(0.36-5.9)
7	PAIS (46XY)	F	14	Mucinos cystadenoma	No	No	No	No	No	Yes	Abdominal mass	Testis	13(<0.07-0.75)	30(<0.02-16.7)	2.7(0.9-8.9)	16.4(15-350)	250(0.49-6.9)

S / N	DSD Diagnoses	Sex	Age	Malignant Tumor	Tumor Stage	Elevated tumor marker	Malformation	obesity	Gonadectomy	Psychosocial issues	Presentation	Gonadal tissue	Total Testosterone (ng/ml)	LH (UI/L)	FSH (UI/L)	Estradiol (pg/ml)	AMH (ng/ml)
1	Turners Syndrome (45X)	F	10	Dysgerminoma	1	Yes	Short, short neck, hydronephrosis	yes	yes	No	Short,	Ovary	*0.07(<0.07-0.44)	21(<0.02-4.8)	43(0.5-6.0)	*8(≤24)	1(0.36-5.9)
2	Sywer Syndrome (46XY)	F	1	Yolk	1	Yes	Strabismus, congenital inguinal hernia	No	Yes	No	Abdominal pain, mass	Streak gonads	0.04(<0.07-0.20)	1(<0.02-0.3)	6.4(0.5-6.0)	*5.2(≤20)	Undetected (0.11-4.2)
3	CAIS (46XY)	F	<1	Dysgerminoma	1	No	Septal nasal defect	Yes	Yes	No	Abdominal pain	Testis	0.3(<0.07-0.20)	20(<0.02-18.3)	3(1.2-12.5)	*6.5(≤20)	278(0.11-4.2)
4	Turners Syndrome (45X)	F	13	Dysgerminoma	3	Yes	Short, short neck, Scoliosis	Yes	Yes	yes	Abdominal pain	Ovary	0.19(<0.07-0.75)	26(<0.02-11.7)	55(0.9-8.9)	10(15-85)	0.4(0.49-6.9)
5	Klinefelter (XXY)	M	16	Seminoma	1	Yes	Choledochal cyst	yes	yes	yes	Micropens Gynecomastia	Testis	0.72(1-12)	30(0.8-8.7)	41(0.7-9.6)	30(≤38)	*0.6(<13)
6	Sywer Syndrome (46XY)	F	6	Mixed GCT	2	Yes	Short, strabismus	Yes	yes	No	Abdominal mass	Streak gonads	0.03(<0.07-0.20)	1.1(<0.02-0.3)	20(0.5-6.0)	*5.9(≤20)	Undetected (0.21-4.9)
7	5-alpha reductase deficiency (46XY)	F	14	Granulosa cell tumors	2	No	Thyroid dysgenesis	Yes	Yes	yes	Amenorrhea. hypothyroidism	Testis	4.4(<0.07-0.75)	7(<0.02-16.7)	3.2(0.9-8.9)	20(15-350)	13(0.49-6.9)
8	PAIS (46XY)	F	14	Dysgerminoma	4	No	Hydronephrosis, astigmatization (myopic)	Yes	Yes	No	Abdominal mass	Testis	11(<0.07-0.75)	37(<0.02-16.7)	4(0.9-8.9)	15(15-350)	300(0.49-6.9)
9	5-alpha reductase deficiency (46XY)	F	15	Immature Teratoma	2	Yes	short neck, cleft palate retrognathia, short, ASD Clubfoot down syndrome, tracheomalacia, strabismus,	Yes	Yes	yes	Amenorrhea, micropenis	Testis	5.8(<0.07-0.75)	8.6(<0.02-16.7)	4.5(0.9-8.9)	16.2(15-350)	3.2(0.62-7.8)
10	congenital adrenal 21 hydroxylase (46,XX)	M	13	Immature Teratoma	3	Yes	No	yes	yes	yes	Abdominal pain,	Ovary	10(<0.07-8)	2.5(0.1-5.7)	3.9(0.6-6.9)	14(≤26)	*3(<13)

Table 2. The clinical finding of the children with disorder of sex differentiation and gonadal tumors in the study

Our management approach for DSD patients with gonadal tumors is shown in Figure 4.

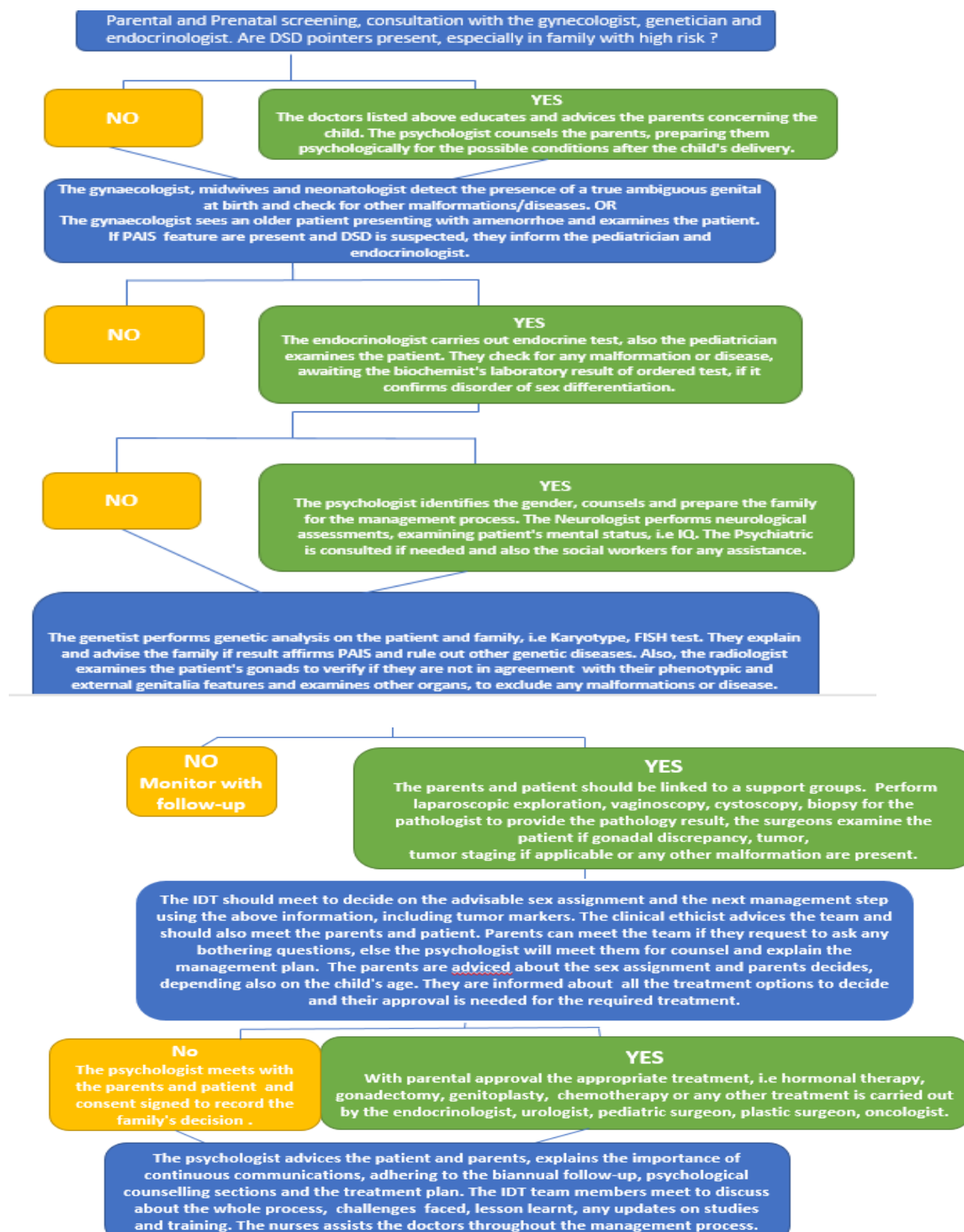


Figure 4. Our management approach for DSD patients with gonadal tumors.

CONCLUSION

In conclusion children with disorders of sex differentiation, have a higher risk of malignant gonadal tumors, especially if having other risk factors such as obesity and systemic malformation, also psychosocial issues were associated with pubertal age (>12 years) in this study. Diagnosis of DSD, especially at puberty raised numerous challenges that can affect achieving the treatment management; hence early diagnosis is preferred. Communication is important among the interdisciplinary team, as well as the psycho-emotional stability of the child with DSD and their family is crucial. Cytogenetic and molecular genetic testing is important in the management of patients with gonadal tumors or /and DSD.

