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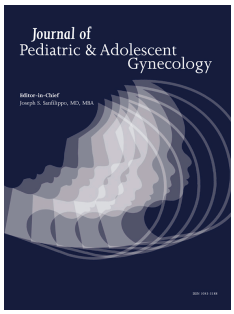

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A pre-operative scoring system for adnexal mass in children and adolescents to preserve their future fertility

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Abstract

STUDY OBJECTIVE: To develop a predictive score for ovarian malignancy to avoid unnecessary adnexectomy in cases of adnexal mass in pediatric and adolescent girls.

DESIGN: A population-based retrospective study on girls who underwent surgery for an ovarian mass with normal levels of human chorionic gonadotrophin (hCG) and alpha fœtoprotein (aFP) between 1996 and 2016.

SETTING: Rennes University Hospital, Rennes, France.

PARTICIPANTS: Eighty-one patients operated on for ovarian tumor.

MAIN OUTCOME MEASURES: The main outcome measure was the rate of malignant and borderline tumor. A pre-operative scoring system was constructed after multivariate analysis.

RESULTS: The rate of malignant ovarian tumor was 7%, borderline tumor was 9% (i.e., outcome measure: 16%), and benign tumor was 84%. In a univariate analysis, the characteristics significantly associated with malignancy were early puberty, palpable mass, size and content of the tumor, and positive epithelial tumor markers [CA 125, CEA, and CA 19-9]. The predictive malignancy score was based on two variables obtained after multivariate analysis: tumor size and cystic content. The score defined 3 groups at risk for malignancy: low risk, middle-risk and high-risk. The sensitivity for detecting malignancy was 1.3% (95%CI: 0.1–18.4), 26.2% (95%CI: 11.6-49.0) and 53.1% (95%CI: 29.1–75.8), respectively.

CONCLUSION: We set up a simple predictive score of malignancy based on objective criteria to help decision making on whether or not ovarian-sparing surgery is feasible in case of children and adolescents with ovarian tumors and normal hCG and aFP levels while ensuring oncologic safety.

Key words: Adnexal mass, children, adolescent, surgery, ovarian malignancy, score, ovarian preservation.

INTRODUCTION

Ovarian tumors in children and adolescents are rare, with an estimated incidence in girls of 2.2/100,000 [1–3]. The majority of ovarian tumors in this population are benign and often organic; only 10-20% are malignant [4,5]. Among children and adolescents, only 1% of pediatric cancers are malignant tumors of the ovary [4–9]. The age of the child does not change the risk of malignant ovarian tumors. Germ-cell tumors represent most ovarian tumors and include mature benign teratomas (dermoid cysts) [10]. Overall, patients with malignant germ-cell tumors have a good prognosis [11]. Sex-cord stromal tumors are regularly seen in pediatrics. The prognosis of these tumors is related to the initial surgery, which must be complete [12].

The discovery of an ovarian mass in a child presents a dilemma regarding the optimal treatment. An immediate oophorectomy, or adnexectomy, has the best oncological safety, whereas an ovarian cystectomy better preserves the patient's fertility. Indeed, an ovariectomy or adnexectomy in childhood is correlated with a lower spontaneous pregnancy rate (45,5%) [13,14] and premature ovarian failure [15], which is an ongoing concern. Of note, in Western countries, because of societal evolution, pregnancy occurs later, with 22% of births occurring in women over 35 years of age [16]. Thus, women who underwent ovariectomy in childhood are particularly vulnerable to ovarian failure at the time of conception, and ovarian preservation in children is crucial to protect their future fertility. However, oncologic surgery remains mandatory for the treatment of ovarian cancer to avoid compromising an otherwise good prognosis. Indeed, the main risk of ovarian-sparing surgery in case of malignant germ cell tumor is either spillage or recurrence on the preserved parenchyma [10,17].

The rates of conservative surgery for ovarian mass in pediatric patients are from 18% to 72% [1,18–20] depending on surgeon habits and cohort studies, reflecting the fact that a majority of benign adnexal masses in children are removed via oophorectomy. Preoperative analysis of the lesion remains crucial for tailoring surgical management, i.e., appropriately choosing

between oophorectomy and ovarian conservative management [21]. Although International Ovarian Tumor Analysis (IOTA) classification for adnexal masses is available for adult women [22], there are no objective criteria or reproducible tools to preoperatively predict the risk of malignancy in children with an adnexal mass.

The aim of this study was to determine the predictive factors of malignancy in pediatric patients with an adnexal mass and to develop a simple score for predicting malignancy.

METHODS

Objective and design of the study

This was a population-based retrospective study conducted from January 1996 to April 2016 in a tertiary hospital (Rennes Teaching Hospital, France). Inclusion criteria were patients aged 0 to 18 years with a diagnosis of ovarian mass who underwent surgical treatment. Exclusion criteria were positive germinal tumor markers: alpha-fetoprotein (αFP) > 10 ng/mL, human chorionic gonadotropin (HCG) > 5 mU/mL or a functional follicle on sonography or pathological analysis. Indeed, positive germinal tumor markers are always associated with a malignant germ cell tumor [4,11,23,24]. We differentiated germinal tumor markers (αFP and HCG) from epithelial tumor markers (cancer antigen (CA) 125 (CA125), carcinoembryonic antigens (CEA), and CA 19-9).

The main outcome measure was defined as the finding of ovarian cancer or a borderline ovarian tumor on the final pathological analysis because these findings usually required adnexectomy. Ovarian borderline lesions were diagnosed upon pathological analysis according to the 2014 World Human Organization criteria [25], as was ovarian cancer. All final pathological analyses were reviewed by a certified pathologist (SH).

This study was approved by the local Institutional Review Board (CEROG 2016-GYN-1003).

Data collection

The medical database from the pediatric surgery department was used to select the patients. The data were collected from the patients' medical records, which were stored in the hospital's archiving system. Data regarding the patient's age at diagnosis, hormonal status (puberty, defined by the presence of a menstrual cycle), medical history, and clinical symptoms were collected. According to the symptoms, a palpable mass was defined as the

palpation of a mass by the patient or her physician, or as an increase in the abdominal perimeter observed by the patient.

The characteristics of the ovarian lesions were obtained from preoperative imaging [ultrasound, abdomino-pelvic computed tomography (CT) and/or pelvic magnetic resonance imaging (MRI)] and described according to the International Ovarian Tumor Analysis (IOTA) classification [22] for pelvic ultrasound using the following ten criteria: maximum diameter of the mass, the presence of a septum, the regularity of the wall, type of cyst (multilocular, solid multilocular, unilocular, solid unilocular, solid), cyst content, solid papillary projection, posterior shadow cone, Doppler signal strength, and the presence of ascites or a peritoneal implant. All preoperative imaging were reviewed by a certified specialist in the imaging of the female reproductive system who was blind to the final pathological analysis.

Data regarding elevated levels of tumor markers [αFP > 10 ng/ml, HCG > 5 mU/ml, CEA > 30 µg/L, cancer antigen CA125 > 35 U/ml, and CA19-9 > 37 U/ml], the type of surgery performed, association with an adnexal torsion, complications of the surgical procedure, and pathological findings were also collected.

The lesions were classified as benign and non-benign comprising borderline and malignant tumours.

Statistical analysis

For quantitative variables, data were expressed as mean ± standard deviation (SD) if normally distributed and median (min-max) if not normally distributed. For qualitative variables, data were expressed as n (%). Comparisons between groups were performed using t-tests for normally distributed variables, Wilcoxon for non-normally distributed variables and chi-square test or fisher exact test for categorical variables. A forward logistic regression analysis was applied to the statistically significant variables to test their association with malignancy. All

variables for which statistical significance was <0.2 were introduced into models. Optimal cut-off values were obtained by optimization of the Younden index from AUROC curve analysis. The predictive malignancy score was constructed from variables derived from the multivariate analysis. Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) were also calculated. A P value of <0.05 was considered statistically significant. Statistical analyses were performed using SAS V9.4 (SAS Institute, USA).

RESULTS

An adnexal mass was detected in 89 children during the study period. One patient was excluded because of follicle diagnosis, and seven others were excluded because of high levels of serum αFP and HCG, which are known positive markers of germinal tumor (figure 1). All seven of these patients underwent ovariectomy surgery and final ovarian germinal tumor diagnosis. Finally, 81 patients were included in the study.

Descriptive data

The characteristics of the patients are summarized in Table 1. The mean (± standard deviation) age of the population was 13.1 (± 4.7) years, without significant difference between the two groups (p=0.40). There were 36 (44%) right ovarian masses and 45 (56%) left ovarian masses. There were 4 (31%) malignant tumors and 26 (38%) benign tumors among the pre-pubescent patients (p=0.76).

Laparotomy was performed in 20 patients (25%), while 61 (75%) underwent laparoscopic surgery, including 22 conversions to laparotomy. Among these 22 patients with conversions, one tumor was borderline, and 21 were benign (7 adnexal masses had a size > 100 mm). Finally, 42 (52%) laparotomies were performed (32 horizontal and 10 median laparotomies) for 30 benign tumors (44.1%) and 12 malignant tumors (92.3%) (p<0.0001).

Of note, there were 14 adnexal torsions, all due to a benign mass. Ten underwent a non-conservative treatment and 4 either tumorectomy or isolated adnexal detorsion.

The pathological results are presented in Table 2. Briefly, seven patients had an epithelial borderline ovarian tumor and six had ovarian cancer (five non-epithelial tumors and one epithelial tumor). Thus, 13 (16%) of the 81 patients had an adnexal tumor that required oncologic surgical treatment, i.e., non-conservative treatment (primary outcome measure).

In the present study, all patients with malignant tumors were treated with non-conservative surgery (oophorectomy or adnexectomy), and 3 out of the 7 patients with borderline tumors underwent cystectomy.

Data analysis

Symptoms were significantly associated with malignancy (p=0.01), especially early puberty and palpable mass (Table 1).

Preoperative ultrasound was performed for 79 patients; 24 patients underwent CT, and 22 underwent MRI. The size of the lesion was significantly associated with malignancy ($p < 0.0003$) as all malignant lesions exceeded 65 mm in diameter with a mean size of 166.1 mm (70.3) vs. 86.3 mm (63.9) for benign lesions in the univariate analysis. A lesion size > 100 mm following the IOTA classification's cut-off was correlated with ovarian cancer ($p = 0.003$) as determinate in a univariate analysis (Table 1).

Among the morphological criteria used in echography to characterize a malignant tumor, the type of ovarian mass was significantly associated with malignancy (p=0.002). In this study, a solid multilocular mass was identified in 5/13 (38%) patients with malignant tumors vs. 5/68 (7%) patients with benign tumors (Table 1).

Tumor markers were significantly associated with ovarian malignancy ($p = 0.009$) and were measured in 64/81 (79%) patients. Tumor markers were elevated in 7/13 (54%) patients with malignant tumors vs. 9/51 (17%) patients with benign tumors.

Based on 72 patients who underwent preoperative sonography, the multivariate analysis defined two predictive factors of malignancy and borderline tumor: the size of the tumor (<65mm, between 65-130mm, >130mm) and the ultrasound aspect of the tumor (unilocular cystic tumor or not) (Table 3).

Malignancy scoring system

A predictive score for malignancy (Table 4) was constructed using the two variables associated with malignant ovarian tumor or borderline tumor derived from the multivariate analysis. A receiver operating curve (ROC) was plotted to determine the sensitivity and specificity of the score (Figure 2). The area under the curve (AUC) of the ROC was 0.88 [0.80 – 0.95].

Following the IOTA recommendations with a single cut-off at 100mm, the multivariate Odd Ratio was 7.68 (1.96-30.07). To maximize the statistical significance of the "lesion size" variable we selected two cut-offs: 65mm and 130mm. The choice of two cut-off points to define a population at low risk (<65mm) and a population at high risk (>130mm) provided a clinical prediction rule with a good diagnostic performance: the low risk cut-off point defined a model with a sensitivity of 100% and the high risk cut-off point defined a model with a specificity of 88%.

The score was constructed from the logistic model coefficients (Table 4). Using a score cut-off >25, the sensitivity, specificity, positive predictive value and negative predictive value for predicting malignancy were 100%, 63%, 37% and 100%, respectively.

Clinical utility of the score

The score stratified the population in 3 groups at low-risk, middle-risk and high-risk of malignancy. This was applied to our study population following the rules that low-risk was due to ovarian-sparing surgery, high-risk to non-sparing surgery and middle-risk to further investigations or discussion. This resulted in 46 (57%) patients who should be spared adnexectomies, 16 (20%) patients who would have been referred for non-conservative treatment, and 19 (23%) who would have required more investigations and discussion on the risk and benefits of each option. This led to 80% of non-radical first line treatment (conservative treatment or implement investigations).

DISCUSSION

In the present study, we created a simple score for predicting malignancy in children and adolescents with adnexal mass and therefore helping to determine whether conservative or radical surgery is the optimal treatment strategy. We built a scoring system using factors found in the multivariate analysis: tumor size and cyst component. This tool provides ensured oncologic safety while preserving fertility. In our series, fertility would be directly spared in 57% of children with adnexal mass, and 23% of the patients would require more investigations before taking the decision on ovarian sparing surgery. All patients with ovarian cancer (borderline or invasive) would undergo either non-conservative surgical treatment or continuation of the work-up, which is, at present day, the correct oncologic decision.

Some weaknesses of present study must be mentioned, particularly in relation to the misinterpretation of data, classification bias, or missing data because of the study's retrospective nature. Nevertheless, our results are similar to those previously reported in populations ranking from 41 to 112 patients with a malignancy prevalence of malignancy between 10 to 20%. This prevalence might vary depending on the age at screening and the availability of tertiary screening centers. Conservative surgery ratios vary between 15% and 87% according to recent studies [1,18–20,26].

Many studies have sought to identify predictive characteristics to guide the decision of conservative vs. radical surgery [17,27–30]. The detection of αFP and HCG (marker of germinal tumor) in blood testing strongly indicated that the tumor is malignant, which is why patients with positive germinal markers were excluded from our study because required non-conservative surgical treatment for oncologic purpose. To predict whether a tumor might be benign or malignant, its characteristics are determined using pelvic echography or MRI. For example, tumors > 7.5-8 cm are at high risk of being malignant, according to published data [19,26,27,31]. The threshold varies depending on the studies and specificity and sensitivity levels

chosen: in the present study, a tumor size correlated with malignancy was 65 mm or larger (as much as 100 mm or more). As opposed to adult women, there is no classification dedicated to the pediatric population to differentiate benign from malignant tumors based on their ultrasound features (or MRI features). Thus, in present study, we used IOTA classification to sort and interpret preoperative sonography pictures [22,32]. Using the simple rules proposed by the IOTA classification, our study showed first that solid multilocular ovarian mass is significantly associated with malignancy in children.

The Ueland Index, described by Stankovick, is an ultrasonographic algorithm tool specific to the pediatric population [33,34]. Its two criteria are the volume and structural characteristics of the tumor. A tumor is considered benign if it is < 5 cm and malignant if > 7 cm in diameter. This tool predicted the risk of malignancy with a sensitivity of 90% and a specificity of 94%. In another recent study, Stankovic showed that discrimination between benign and malignant tumors in pediatric and adolescent patients was greater with the Ueland index than with the search for the ovarian crescent sign (OCS). Indeed, there is a lack of reproducibility in the ultrasonographic search for the OCS [35], as it is difficult to spot when the mass is > 5 cm in abdominal echography; therefore, it is unreliable as a discriminating sign. Nevertheless, the Ueland Index had some weakness because it was determined as an algorithm and not based on a statistical tool, such as logistic regression, as our proposed robust score. Both our score and the Stanakovic algorithm still require external validation using multicenter prospective cohort.

Despite previous studies have shown that size and complexity were important predictors of malignancy [19,20,26,36,37], none of the different scoring system or preoperative stratification has proven its clear utility. For example, following the recommendations published by Rogers et al [20], 15 patients in our series would have had a malignant tumor management because of the size>8cm of their ovarian masses. We also applied the preoperative risk stratification described by Madenci et al in 2016 on our series[36]. This led to 54.5% ovarian sparing surgery,

10% non-sparing surgery and 35.5% of doubtful cases. Our score led to 57%, 20% and 23% respectively. In their series, Madenci et al [36] reported less malignant tumors (8% vs 16%) and included functional cyst (23%) that we did not consider as ovarian tumors and were excluded in our study. As stated in many studies, every case should be unique and discussed between family and surgeons. Thus, we propose a simple score to add an objective value to the discussion and decision-making and improve the armamentarium that helps dealing with ovarian tumors. Using this score in a daily manner would be easier and less tedious than following most of the risk stratifications previously described. In practice, when seeing children with adnexal mass, physicians should perform an ultrasound scan and the usual work-up with tumor markers. In case of confirmed ovarian tumor with negative αFP and HCG, one could apply this scoring system and adapt the strategy and the speech given to the family following the predictive risk described in Table 4. Patients in the low-risk group could undergo ovarian-sparing surgery, when possible after an MRI to guide the surgery. In the middle-risk group, a complementary work-up comprising at least an MRI should be mandatory taking into account the 26% predictive risk of malignancy. Patients belonging to the high-risk group should be proposed a non-conservative treatment.

In our study, 10 out of 14 adnexal torsions were treated with oophorectomy or adnexectomy. Since the introduction of the national or international recommendations in the gynecologic society [38,39], this treatment strategy has to change. The revised approach is based on the recognition that even if the ovary has an infarcted appearance, it may recover normal endocrine function [13]; thus, conservative treatment should be attempted in all cases [40–42]. Indeed, in our study, adnexal torsion was never associated with a malignant or borderline tumor, as confirmed by published data[13,40].

In the literature, the specialty of the surgeon was shown to influence the decision for ovarian preservation [31,43] with more conservative treatments performed by gynecologic surgeons and

less conservative treatment performed by a pediatric surgeon. This difference in care outcome should be addressed. By using the score evaluated in this study, the probability of malignancy can be better evaluated preoperatively, allowing a better-informed decision regarding ovarian preservation. Our score allowed 57% of ovarian conservative surgeries and 23% of patients requiring more investigations. The ovarian-sparing surgery rate must be improved in the future and we need to work with radiologist to improve the care of the 23% of doubtful cases. It is likely that adnexal mass in children should be explored systematically by MRI combined with perfusion- and diffusion-weighted MR imaging as used in adult women with ovarian mass [44]. These new tools must be validated in children to improve the ovarian conservation rate in case of adnexal mass since these approaches have only been recently described [45,46]. It could also help to visualize healthy ovarian tissue remnants in case of large tumors.

CONCLUSION

To our knowledge, this is the first published simple scoring system for predicting malignancy in children and adolescents with an adnexal mass. It is based on easily obtained sonographic data (size and echogenicity of the tumor) and can be applied in children with an adnexal mass and normal germinal tumor marker levels. The score could be used to guide decision-making regarding conservative vs. non-conservative ovarian surgical treatment and may therefore increase the rate of fertility preservation while ensuring good oncologic safety in a larger number of patients. In our study, 80% of the children with an adnexal mass may undergo ovarian-sparing surgery (57% of first line conservative treatment and 23% requiring more investigations before decision) based on reproducible criteria. However, this scoring system still requires external validation in a prospective multicenter study before it can be routinely

used in a clinical setting. MRI combined with perfusion- and diffusion-weighted MR imaging applied to the pediatric population could be the next step in improving the rate of ovarian preservation surgery in children with adnexal mass. Of note, conservative management in cases of adnexal torsion in children, as in adults, will also help to increase the rate of ovarian-sparing surgery.

Disclosure of interest statement: Nothing to disclose.

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Table 1: Preoperative patient characteristics

Table 2: Pathologic findings of pediatric ovarian masses

Table 3: Predictive factors of malignancy and borderline tumors in the multivariate analysis

OR, odds ratio, CI, confidence interval

Table 4: Score predictive of malignancy

Figure 1: Flow chart

Figure 2: ROC curve of the score to predict malignancy

	Study population N = 81	Malignant tumor N = 13 (16%)	Benign tumor N = 68 (84%)	p-value
Age				
Age (y), mean ±SD	13.1 ±4.7	13.8 ±5.2	13 ±4.6	
Age (y), median (min-max)	15 (0-19)	15 (3-18)	15 (0-19)	0.40
0 to 8	15 (19%)	2 (15%)	13 (19%)	0.68
9 to 13	14 (17%)	1 (8%)	13 (19%)	
>13	52 (64%)	10 (77%)	42 (62%)	
Hormonal status				
- Pre-pubescent	30 (37%)	4 (31%)	26 (38%)	0.76
BMI				
- Mean ±SD	21.7 ±3.6	20.6 ±3.0	22.0 ±3.7	0.41
Symptoms				
Palpable mass	13 (16%)	4 (31%)	9 (13%)	**0.01**
Acute pain	49 (60%)	6 (46%)	43 (63%)	
Other	17 (21%)	1 (8%)	16 (24%)	
Early puberty	2 (2%)	2 (15%)	0	
Sonography size				
Size (mm), mean ±SD	99.1 ±70.9	166.1 ±70.3	86.3 ±63.9	
Size (mm), median (min-max)	70 (19-360)	170 (65-260)	66 (19-360)	**0.0003**
>100 mm	30 (37%)	10 (77%)	20 (29%)	**0.003**

Type of ovarian mass				
Multilocular	7 (9%)	2 (15%)	5 (7%)	
Solid multilocular	10 (12%)	5 (38%)	5 (7%)	
Unilocular	36 (44%)	3 (23%)	33 (49%)	**0.002**
Solid unilocular	27 (33%)	2 (15%)	25 (37%)	
Solid	1 (1%)	1 (8%)	0	
Sonography characteristic				
Solid	38 (47%)	8 (62%)	30 (44%)	0.25
SPP*	37 (50%)	4 (44%)	33 (51%)	1.00
Calcification	20 (25%)	2 (15%)	18 (27%)	0.79
Cystic	29 (40%)	3 (23%)	26 (44%)	0.16
Ascites	4 (5%)	2 (15%)	2 (3%)	0.16
Peritoneal implant	1 (1%)	1 (8%)	0	0.17
Tumor markers				
Positive marker	16 (24%)	7 (54%)	9 (17%)	**0.009**
CA 125	13 (16%)	6 (46%)	7 (10%)	**0.005**
CA 19-9	7 (9%)	3 (23%)	4 (6%)	**0.038**
ACE	2 (3%)	2 (15%)	0	**0.027**
Torsion	14 (17%)	0	14 (21%)	0.11

Table 1: Preoperative patient characteristics

Pathologic	Patients	%
Benign	**68**	**84**
Germ-cell tumor	**42**	
Mature teratoma	42	
Epithelial	**24**	
Serous cystadenoma	16	
Mucinous cystadenoma	8	
Sex-cord stromal tumor	**1**	
Sclerosing tumor	1	
Indeterminate tumor	**2**	
Borderline	***7***	***9***
Serous	3	
Mucinous	4	
Malign	**6**	**7**
Germ-cell tumor	**2**	
Dysgerminoma	1	
Immature teratoma	1	
Epithelial	**1**	
Mucinous cystadenocarcinoma	1	
Sex-cord stromal tumor	**2**	
Juvenile granulosa tumor	2	
Secondary	**1**	

Table 2: Pathologic findings of pediatric ovarian masses

N=72	Malignant & borderline (N=13)	Benign (N=59)	Multivariate OR (95% CI)
Size <65 mm	0	27 (46%)	1
65<size<130 mm	5 (38%)	25 (42%)	10.89 [0.57–210.0]
Size>130 mm	8 (62%)	7 (12%)	74.54 [3.58–999.99]
Unilocular cystic tumor	3 (23%)	26 (44%)	1
Other type of tumor	10 (77%)	33 (56%)	3.63 [0.74–17.84]

Table 3: Predictive factors of malignancy and borderline tumors in the multivariate analysis

OR, odds ratio, CI, confidence interval

Variable	Score	Predictive risk (95% CI)
Size of lesion (mm)		
<65	0	
65 – 130	25	
>130	41	
Unilocular cystic tumor		
Yes	0	
No	9	
Total score		
Low-risk group	0 - 25	1.3% [0.1–18.4]
Middle-risk group	26 - 40	26.2% [11.6-49]
High-risk group	>40	53.1% [29.1–75.8]

Table 4: Score predictive of malignancy

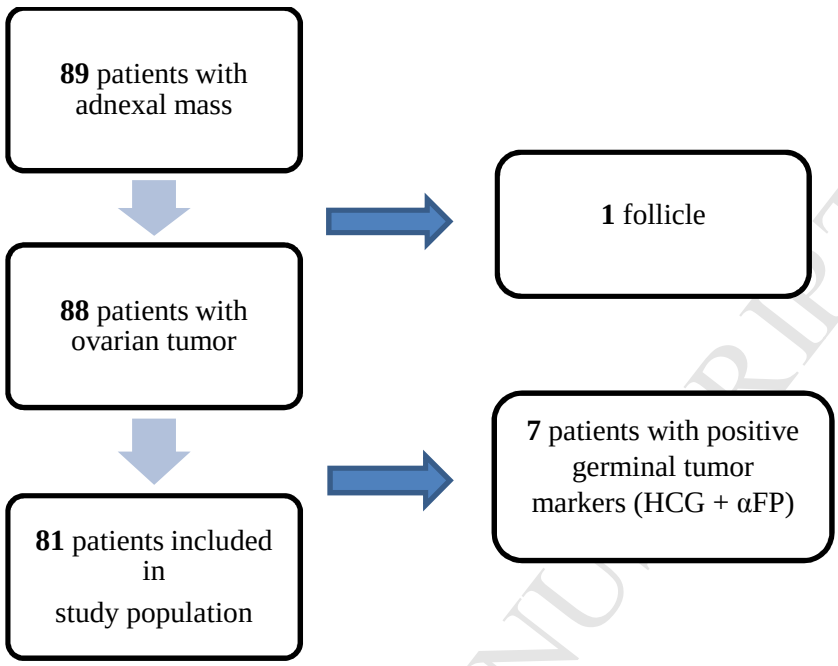

Figure 1: Flow chart