의학석사 학위논문

Prepubertal testicular tumors in Korea
: a single surgeon experience
of more than 20 years

단일 술자에 의한 수술 사례 분석을 통한
한국의 사춘기 이전 고환암의 현황

2014년 2월

서울대학교 대학원

임상의과학과

백 경 돈

Master's Degree Thesis

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Prepubertal testicular tumors in Korea : a single surgeon experience of more than 20 years

February 2014

Department of Clinical Medical Sciences,

Graduate School

Seoul National University

College of Medicine

Kyung Don Baik

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지도 교수 박 관 진

이 논문을 의학석사 학위논문으로 제출함

2013년 12월

서울대학교 대학원

임상의과학과

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백경돈의 의학석사 학위논문을 인준함

2013년 12월

위 원 장 이 상 민 (인)

부위원장 박 관 진 (인)

위 원 지 의 규 (인)

Abstract

Introduction:

To provide clinical and histological features of prepubertal testicular(PTT) through the analysis of long – term experiences of single surgeon

Methods:

Charts were retrospectively reviewed in 48 children who were treated for testicular tumors from 1986 to 2010. All patients underwent radical orchiectomy. The patients′ age, clinical presentation, histopathological findings, kinetics of tumor marker and outcome were recorded.

Results:

The median age at initial diagnosis was 19.5 (3-84) months. All patients were presented either palpating mass (76%) or scrotal size discrepancy (24%). Compared to palpating mass, scrotal size discrepancy led to delay in diagnosis by 5 months. Regarding histology, yolk sac tumor and teratoma accounted for 53% and 36% of the patients, respectively. The mean preoperative AFP was significantly higher in yolk sac tumor than teratoma (4,600 ng/ml vs, 6.3ng/ml) and only one case of teratoma showed their preoperative AFP more than 20 ng/ml. Following the radical orchiectomy, 72%, 8% and 16% patients with yolk sac tumor showed normalization, persistent elevation and relapse after transient lowering of AFP, respectively. Preoperative AFP was greater in patients with non-normalization than those with normalization. Five out of six patients with non-normalization showed the evidence of either vascular invasion or endolymphatic tumor emboli.

Conclusions:

Our experience showed the higher number of yolk sac tumor than teratoma. AFP was found to be the most useful marker in the diagnosis and follow-up of childhood yolk sac tumor. Relapsed yolk sac tumor often showed pathological evidence of aggressiveness.

Keywords: Testicular tumor, Prepubertal, Racial difference
Student Number: 2012-22698

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Introduction

Prepubertal testicular tumors (PTT) are rare disease, representing 1% to 2% of all pediatric solid tumors and its annual incidence is 0.5 to 2 per 100,000 children.(1) Most information regarding PTT are based on the experiences with adult counterpart, however recently published data indicated that PTT were distinct from postpubertal tumors with regard to histological distribution, clinical course and management algorithm.(2-5) For instance, while seminoma or mixed histology are dominant in adult testicular tumors, PTT are mainly comprised of teratoma or yolk sac tumor.(2)

Regarding PTT, the distribution of histological types still remains controversial. While yolk sac tumor has been known as the most common PTT,(2) growing number of recent studies indicated that teratoma were more frequent than yolk sac tumor in PTT.(3-5) Some speculated this disparity as racial differences based on genetic or environmental discrepancies, while others believed that it was just reporting bias.(6-8) Since the recent data of PTT showing the predominance of teratoma reflect the case of western countries, the explanation of racial difference looks plausible and should be verified. Unfortunately, only a few Asian data are available, making direct comparison difficult.(9-11)

Serum alpha fetoprotein (AFP) has been widely used to evaluate the patients with PTT. Its elevation usually reflects the presence of components of yolk sac tumor, but it is neither sensitive nor specific to yolk sac tumor(Fig.1). For example, the elevation of AFP is well known in benign teratoma and even in normal infant. This may create the problem in considering testis sparing surgery for benign teratoma. Since there are no reliable US criteria for diagnosing benign vs malignant testis lesions, the understanding

of the possible range of AFP in a specific tumor that may differentiate benign teratoma from yolk sac tumor would be beneficial in preoperative planning.

Also, serum AFP is believed to be useful in monitoring the treated patients with yolk sac tumor. However, due to the small number of the patients, little data has been present in regards to the fate of the patients who fails to achieve or maintain normalization.

To address the aforementioned issue, we analyzed our experience of 22 years. We believed that this kind of single institutional study has an advantage that all pathology and clinical data can be tracked and analyzed in a similar fashion, minimizing reporting bias. Through this report, we investigate the incidence of yolk sac tumor and teratoma. And we will ensure role of AFP in current diagnostic, treatment and follow up algorithms.

Materials and Methods

Following approval of institutional review board, we obtained the medical records of 52 prepubertal patients less than 12 years of age, who were treated for testicular tumors at Seoul National University Children's Hospital (SNUCH) from 1986 to 2010. Among them, the records of 48 patients had complete pathologic and follow-up data, being eligible for review. The various parameters, such as, age at operation (month), initial presentation, duration of initial presentation to diagnosis, pre and post-operative alpha-fetoprotein (AFP), beta-subunit of human chorionic gonadotropin (β-hCG), evaluations for the preoperative metastatic lesions, clinical stage, histological type, adjuvant therapy and its response, and follow-up periods were studied. Diagnosis and treatment algorithm in SNUCH are following: patients suspicious of testicular tumor were assessed by tumor markers (AFP, β-hCG) and scrotal ultrasonography with plain x-rays. In case of suspicious malignancy, abdomen computed tomography (CT) was obtained to evaluate the retroperitoneal lymph node and/or distant metastasis. And then, all patients were conducted radical inguinal orchiectomy and pathologic results were obtained. Further management was determined in accordance with tumor histology and stage. All patients with stage 1 yolk sac tumor were followed with regular measurement of serum AFP levels.

The Statistical Package for the Social Sciences, version 12.0 (SPSS Inc, USA) was used for the statistical analysis. All clinical parameters were analyzed by the Chi-square, Mann-Whiteny U test and are reported as median values with range. *P* value of less than 0.05 was considered to be statistically significant.

RESULTS

A summary of the clinical data of the 48 patients is listed in Table 1. The median age at diagnosis was 19.5 (3-84) months. Three-quarter of patients were presented due to palpable mass and the remained ones were detected by size discrepancy. The former preceded the latter by 5 months in comparison of mean time to diagnosis (2.5 vs 7.5, $p<0.05$).

The tumors were right sided in 21 (44%) boys and left sided in 27 (56%). Preoperative staging indicated that the 45 (93.8%) of patients were localized tumor without lymph node or distant metastasis. Pathology revealed 25 (53%) yolk sac tumor, 17 (36%) teratoma, 2 (4.2%) embryonal carcinoma, 2 (4.2%) epidermoid cyst, 1 (2.1%) mixed germ cell tumor and 1 (2.1%) fibrosarcoma (Table 2). Twenty-three (92%) patients with yolk sac tumor were stage I at the time of diagnosis.

Table 3 shows the comparison of clinical variables between yolk sac tumor and teratoma. Only mean preoperative AFP differed significantly between the two. The AFP level of yolk sac tumor showed significantly higher than that of teratoma. Given that the normal range of AFP is less than 20ng/ml, all patients with yolk sac tumor showed supranormal values, whereas only one patient in teratoma arm showed higher AFP value than norm. The patient was 17 month-old boy and his preoperative AFP at the diagnosis was 39ng/ml.

Median follow-up period was 62 (1-192) months. With regard to the AFP responses of yolk sac tumor, 18 patients (72%) had normalized following radical orchiectomy, 2 patients (8%) showed persistent elevation of AFP and 4 patients (16%) relapsed after normalization of AFP, and 1 patient was lost follow-up during the period of present

study. Median time to relapse of AFP was 8 months (6-12 months). All 6 patients who showed either elevation or relapse of AFP received salvage chemotherapy. This therapy rescued all but 1 patient and the 1 patient were further treated by peripheral blood stem cell transplantation. No patient has experienced relapse after these treatments.

We finished regular follow up of 3 patients who showed no recurrence for more than 10 years. 2 patients are regularly checked with AFP, CPA & testis SONO. There is no AFP elevation for 6 and 8 years. In the most aggressive case, we did peripheral blood stem cell transplantation(PBSCT) after 10 months of orchiectomy. 2 years later, lung metastasis was detected, so we did metastasectomy & 2nd PBSCT. After the treatment, there is no AFP elevation for 6 years. Now, we have regular follow up every year. (Fig.2)

Comparison of mean preoperative AFP between non-relapsed and relapsed patients revealed that AFP of relapsed patients was greater than those of non-relapsed patients (Table 4). Pathologically, five out of six relapsed patients showed the evidence of either vascular invasion or endolymphatic tumor emboli.

Table 1. Demographics of prepubertal patients with testicular tumor

	N=48
Age (mons) at diagnosis	19.5 (3-84)
Presentation	
mass palpation (%)	36 (75.6)
size discrepancy (%)	11 (24.4)
Duration of presentation to diagnosis (mons)	1.5 (1-31)
Laterality	
Right (%)	21 (45.2)
Left (%)	27 (54.8)
Serum tumor markers	
AFP (ng/ml)	369.5 (1-65,200)
hCG (ng/ml)	2.5 (0.01-2,470)
Localization at initial diagnosis	
locallized tumor (%)	44 (93.6)
LN positive (%)	2 (4.3)
distant metastasis (%)	1 (2.1)
AFP response	
normalized (%)	25 (55.8)
relapsed (%)	4 (9.1)
follow-up loss (%)	5 (11.4)
Follow up period (mons)	36 (1-192)

Table 2. Histologic characteristics and age distribution

Histologic type	No. Pts (%)	Median age at diagnosis (mon)
Yolk sac	25 (53.1)	19 (3-39)
Teratoma	17 (36.1)	17 (7-64)
Epidermoid cyst	2 (4.2)	83.5 (83-84)
Mixed GCT	1 (2.1)	55
Fibrosarcoma	1 (2.1)	77

Table 3. Comparison of yolk sac tumor and teratoma (median value)

	Yolk sac	Teratoma	*P* value
Age	19.0 (3-39)	17.0 (7-64)	0.29
Serum AFP	***4600 (20-65200)***	***6.3 (4-39)***	***0.001*** [†]
Serum hCG	2.5 (0.5-7.9)	2.5 (0.1 -2.5)	0.98

[†] : Mann-Whiteny U test

Table 4. Comparison of clinical parameters between recurrence and non-recurrence in yolk sac tumor

	Recurrence	Non-recurrence	*P* value
No. of patients (%)	7 (29.1)	17 (70.9)	N/A
Age at presentation	16 (10-35)	20 (3-39)	0.63
Serum AFP	***7800 (362-36700)***	***3810 (20-65200)***	***0.04*** [†]
Duration (mo) to nadir	52.5 (30-171)	62 (32-110)	0.52

[†] : Mann-Whiteny U test; N/A, not applicable; mo, months

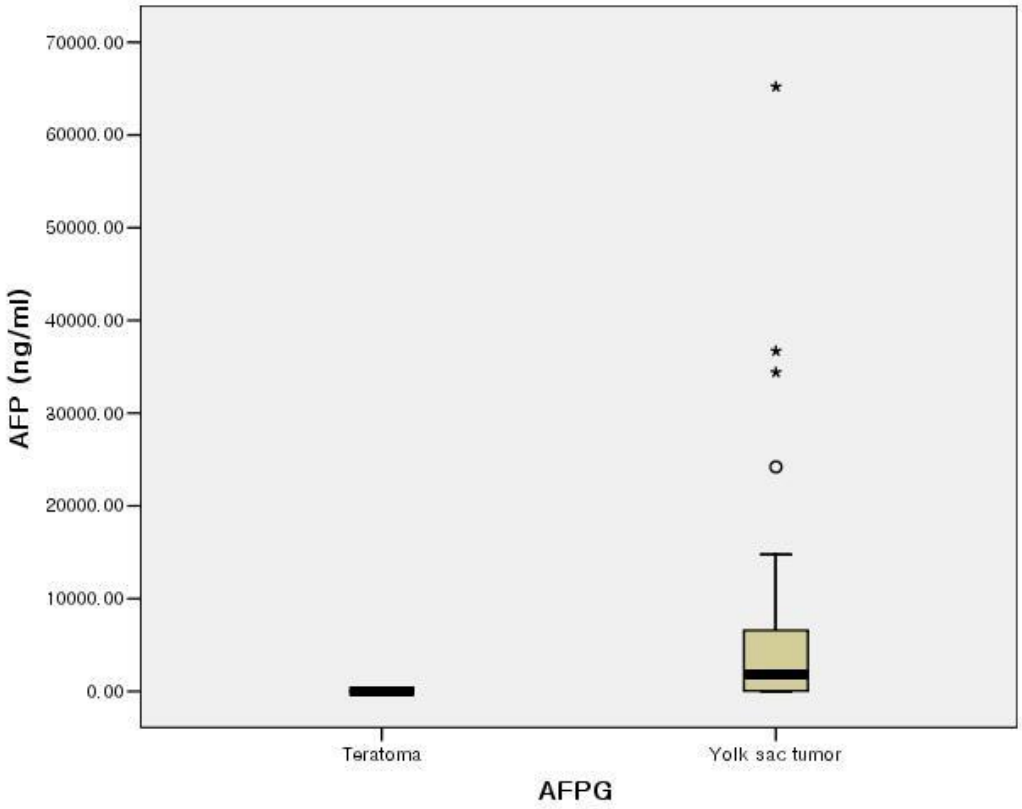

Figure 1. Comparison of preoperative AFP between yolk sac tumor and teratoma

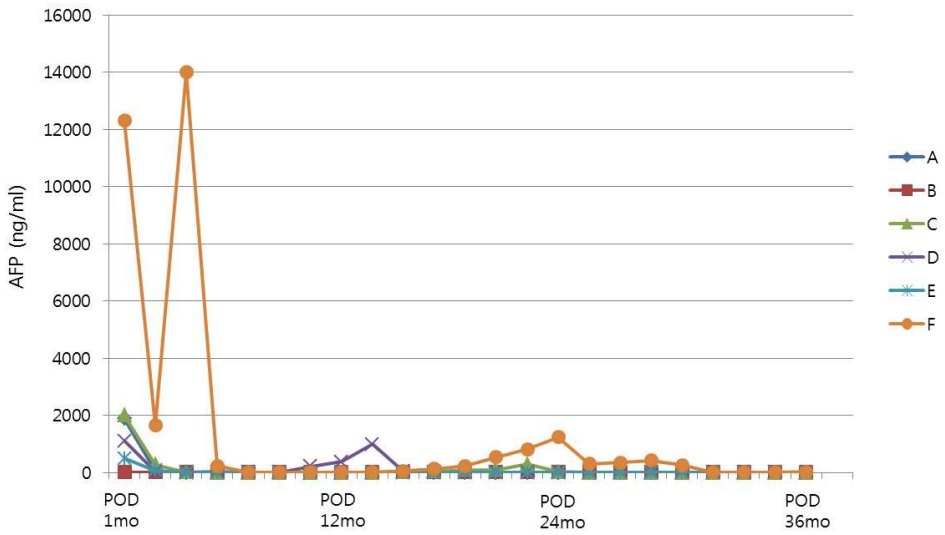

Figure 2. Postoperative AFP patterns in 6 patients who showed persistent elevated or relapsed AFP.

Discussion

This retrospective analysis was conducted in single institutional Korean cohort, which may be useful in reducing reporting bias. Due to the rare worldwide incidence of PTT, we believe that inclusion of our data, despite the small number of cohort, would be the valuable addition to current understanding of PTT. In fact, this study is one of the largest single institutional data of PTT ever reported.

Regarding histological distribution, we confirmed that yolk sac tumor was most prevalent PTT in Korea. Our results are in consistent with that of another multi-institutional Korean study.(9) From the study, the reported rates of yolk sac tumor and teratoma were 48% and 40%, similar distribution to ours, respectively. Moreover, the predominance of yolk sac tumor was reported in Japanese or Taiwanese studies suggesting the predominance of yolk sac tumor in Asian population.(10,11) However, these distributions are in conflict with recently published American data, which showed the larger number of benign teratoma over yolk sac tumor.(3-5) The reason for the discrepancy in histological distribution is still unclear, but some reports provided evidence of racial difference as a possible cause. From the analysis of Surveillance, Epidemiology, and End Results (SEER) data, Walsh et al.(7) found more than 2 fold greater incidence of yolk sac tumor among Asian/Pacific Islanders than whites, whereas no difference in the incidence of teratoma among both ethnic groups. They also reported higher incidence of teratoma than yolk sac tumor in whites and blacks. These may explain the reason of discrepancy of histological distribution among different races. Given the fact that Japanese adults have lower incidence of testis tumor,(8) it is unique that Asian boys are more likely to have yolk sac tumor. Future study will explore what

caused higher incidence of yolk sac tumor in Asian boys.

Our data also revealed that more than 70% of patients were rescued by radical orchiectomy only.) For the remained 6 patients experiencing relapse or persistence of disease, chemotherapy was effective in all but one patient. Although the most aggressive case, there was no need for retroperitoneal lymph node dissection. These contrasted to the reported feature of lymphatic spread and higher metastatic potential of yolk sac tumor in adult counterpart.(12) Prepubertal yolk sac tumors have lower tendency of metastatic disease. Most cases are low stage disease and lymph node is not involved initially. And even if metastasis is presented, it is usually hematogeneous. It means prepubertal yolk sac tumors have lower tendency toward lymphatic metastasis.(13) So routine RPLND or adjuvant chemotherapy are not needed in prepubertal testicular tumors.

In adults, testis tumor is typical example where serum tumor markers play a critical role in diagnosis and management. This is similarly applied to pediatric counterpart and dozens of papers have indicated that AFP has been found to be useful in diagnosing the testis tumor, monitoring the treatment response and detecting recurrence, whereas β-hCG has not.(2,3, 14-16) The present study again confirmed these findings.

Regarding diagnosis, our study underscored the importance of preoperative AFP levels in differentiating yolk sac tumor from teratoma. While all patients with yolk sac tumor showed the elevation of AFP above the reference range (up to 20ng/ml), only one patient with teratoma showed the serum AFP level (39ng/ml) exceeding reference ranges. While there was some overlap of serum AFP level between yolk sac tumor and teratoma, no case of teratoma showed the higher value than 100ng/ml, which was

consistent with the results from Ross et al.(2) If we set 100ng/ml of AFP in differentiating between the two tumors, we would miss only one case of yolk sac tumor confirming the diagnostic value of AFP. This contrasts to other studies, which showed some overlap of APF ranges between the 2 tumors. The reason might be was due to the fact that our teratoma cohort did not include the infant less than 6 months old, which showed physiologic elevation of serum AFP.(17) However, as long as teratoma infrequently affects infants less than 6 months old, the usefulness of AFP in differential diagnosis cannot be denied.

Our results also indicated the usefulness of AFP in monitoring the disease. Following the orchiectomy, six patients who showed the persistence or relapse after normalization of AFP received salvage chemotherapy. This rescued five patients with normalization of AFP. These indicate that measuring AFP only was enough to monitor the fate of testis tumor. While we don't have any solid evidence that elevation of AFP will lead to gross recurrence of yolk sac tumor in PTT, the normalization of AFP after salvage chemotherapy may imply the presence of recurrence and suggest the appropriate management be provided. The importance of monitoring AFP can't be overemphasized in adult's series.(18)

To further know what is related to the patients with relapse, we compared the clinical and pathological characteristics between the relapsed or not to know the predict factors of AFP relapse. Two statistically positive findings were noted. One was that mean preoperative AFP was higher in relapsed patients; however there were considerable overlap between the two, precluding the use of preoperative AFP for predictive purpose. Another was the association of aggressive pathologic behaviors with relapsed patients. It has already been noted that vascular/lymphatic invasion are high-risk factors for

relapse in pure or mixed embryonal carcinoma of adult testis(19) and one Japanese study showed that relapse of yolk sac tumor was associated with the overt invasion of testicular vein.(20) However, our data were the first study to associate the risk of relapse with vascular/lymphatic invasion in PTT. Despite the small number of patients having positive findings, the lack of false positive results would be important in predicting relapse and be helpful in planning follow-up in these low-risk patients.

Some limitation of this study should be mentioned. Due to the small number of specific histology, we did not draw any meaningful conclusion apart from yolk sac tumor and teratoma. In addition, since we only saw the patients with localized yolk sac tumor, we cannot know whether the changes of AFP following treatment might be as good as in yolk sac tumor of other stage. Since the characteristics of tertiary care center, the enrolled patients may not show the histological distribution that can be seen in other hospitals in Korea. Despite all the limitation, we believe that our data would enhance the knowledge of this rare tumor.

Conclusion

Our single center 25 years' experience showed the dominance of yolk sac tumor over teratoma, which is attributable to racial difference that might be originated from genetic factors rather than epidemiologic influence. Compared to adult's counterpart, childhood yolk sac tumor demonstrated more benign course and responded well to chemotherapy even in relapse. In most children, only radical inguinal orchiectromy could be curative. And routine RPLND or adjuvant chemotherapy are not needed. As a differential diagnostic tool, AFP is more useful than image modalities. If AFP is over 100ng/ml, the tumor can be considered closer to the YST than teratoma. So in this case, testis sparing is not indicated. Relapsed yolk sac tumor often showed aggressiveness on pathologic examination and AFP was found to be the most useful marker in the diagnosis and follow-up of childhood yolk sac tumor.

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초 록

서론:

소아의 고환암은 유병률이 매우 낮은 질환으로 그 동안 이에 대한 진단 및 치료알고리즘은 성인의 고환암에 미루어 시행해 왔다. 그러나 성인의 질병과는 병리 특징 및 임상적 과정이 매우 달라 소아 고환암에 대한 정립이 필요한 실정이다. 이에 우리는 지난 20여년 간의 단일 술자에 의한 소아 고환암의 임상적, 병리적 특징을 분석하여 연구해 보고자 하였다.

방법:

1986년부터 2010년까지 고환암으로 진단되어 수술을 시행한 48명의 환아의 의무기록을 후향적으로 분석하였다. 모든 환아들은 근치적 고환 적출술을 시행하였다. 환아의 나이, 임상 양상, 병리적 특징, 종양 표지자의 동역학적인 양상, 치료 결과 등에 대해서 분석하였다.

결과:

진단시 평균연령은 19.5 (3-84)개월이었다. 환아의 주소는 고환 종물이 촉지되어 내원하는 경우가 76%, 양쪽 고환의 크기가 달라서 내원하는 경우가 24%를 차지하였다. 양쪽 고환의 크기가 달라서 내원하는 경우가 고환 종물이 촉지되어 내원하는 경우보다 진단이 5개월 늦었다. 병리적으로는 난황낭 종양이 53%, 기형종이 36%를 차지하였다. 수술전 AFP 수치는 난황낭 종양이 기형종에 비해 매우 높았고(4,600 ng/ml vs, 6.3ng/ml), 기형종에서는

1명의 환아만이 수술전 AFP 수치가 20 ng/ml 이상이었다. 근치적 고환적출술을 시행한 이후 난황낭 종양 환자의 72%는 AFP 수치가 정상화 되었고, 8%는 지속적으로 높은 수치를 보였으며, 16%는 일시적으로 정상화 되었다가 다시 상승하였다. AFP 수치가 정상화되지 않은 환자들의 수술전 AFP은 정상화된 환자들보다 더 높았다. AFP 수치가 정상화되지 않은 6명의 환자중 5명의 환자의 병리 결과 혈관 침범이나 림프종양의 색전 소견을 보였다.

결론:

난황낭 종양 환자가 기형종에 비해 더 많은 수를 차지하고 있는 것으로 나타났다. AFP 은 소아 환자의 난황낭 종양을 진단 및 경과 추적하기에 가장 유용한 도구로 생각된다. 재발하는 난황낭 종양의 경우 병리 소견이 더 악성으로 관찰된다.

주요어: 고환암, 소아, 인종 차이

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의학석사 학위논문

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Department of Clinical Medical Sciences,

Graduate School

Seoul National University

College of Medicine

Kyung Don Baik

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지도 교수 박 관 진

이 논문을 의학석사 학위논문으로 제출함

2013년 12월

서울대학교 대학원

임상의과학과

백 경 돈

백경돈의 의학석사 학위논문을 인준함

2013년 12월

위 원 장 이 상 민 (인)

부위원장 박 관 진 (인)

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Charts were retrospectively reviewed in 48 children who were treated for testicular tumors from 1986 to 2010. All patients underwent radical orchiectomy. The patients′ age, clinical presentation, histopathological findings, kinetics of tumor marker and outcome were recorded.

Results:

The median age at initial diagnosis was 19.5 (3-84) months. All patients were presented either palpating mass (76%) or scrotal size discrepancy (24%). Compared to palpating mass, scrotal size discrepancy led to delay in diagnosis by 5 months. Regarding histology, yolk sac tumor and teratoma accounted for 53% and 36% of the patients, respectively. The mean preoperative AFP was significantly higher in yolk sac tumor than teratoma (4,600 ng/ml vs, 6.3ng/ml) and only one case of teratoma showed their preoperative AFP more than 20 ng/ml. Following the radical orchiectomy, 72%, 8% and 16% patients with yolk sac tumor showed normalization, persistent elevation and relapse after transient lowering of AFP, respectively. Preoperative AFP was greater in patients with non-normalization than those with normalization. Five out of six patients with non-normalization showed the evidence of either vascular invasion or endolymphatic tumor emboli.

Conclusions:

Our experience showed the higher number of yolk sac tumor than teratoma. AFP was found to be the most useful marker in the diagnosis and follow-up of childhood yolk sac tumor. Relapsed yolk sac tumor often showed pathological evidence of aggressiveness.

Keywords: Testicular tumor, Prepubertal, Racial difference
Student Number: 2012-22698

CONTENTS

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Introduction

Prepubertal testicular tumors (PTT) are rare disease, representing 1% to 2% of all pediatric solid tumors and its annual incidence is 0.5 to 2 per 100,000 children.(1) Most information regarding PTT are based on the experiences with adult counterpart, however recently published data indicated that PTT were distinct from postpubertal tumors with regard to histological distribution, clinical course and management algorithm.(2-5) For instance, while seminoma or mixed histology are dominant in adult testicular tumors, PTT are mainly comprised of teratoma or yolk sac tumor.(2)

Regarding PTT, the distribution of histological types still remains controversial. While yolk sac tumor has been known as the most common PTT,(2) growing number of recent studies indicated that teratoma were more frequent than yolk sac tumor in PTT.(3-5) Some speculated this disparity as racial differences based on genetic or environmental discrepancies, while others believed that it was just reporting bias.(6-8) Since the recent data of PTT showing the predominance of teratoma reflect the case of western countries, the explanation of racial difference looks plausible and should be verified. Unfortunately, only a few Asian data are available, making direct comparison difficult.(9-11)

Serum alpha fetoprotein (AFP) has been widely used to evaluate the patients with PTT. Its elevation usually reflects the presence of components of yolk sac tumor, but it is neither sensitive nor specific to yolk sac tumor(Fig.1). For example, the elevation of AFP is well known in benign teratoma and even in normal infant. This may create the problem in considering testis sparing surgery for benign teratoma. Since there are no reliable US criteria for diagnosing benign vs malignant testis lesions, the understanding

of the possible range of AFP in a specific tumor that may differentiate benign teratoma from yolk sac tumor would be beneficial in preoperative planning.

Also, serum AFP is believed to be useful in monitoring the treated patients with yolk sac tumor. However, due to the small number of the patients, little data has been present in regards to the fate of the patients who fails to achieve or maintain normalization.

To address the aforementioned issue, we analyzed our experience of 22 years. We believed that this kind of single institutional study has an advantage that all pathology and clinical data can be tracked and analyzed in a similar fashion, minimizing reporting bias. Through this report, we investigate the incidence of yolk sac tumor and teratoma. And we will ensure role of AFP in current diagnostic, treatment and follow up algorithms.

Materials and Methods

Following approval of institutional review board, we obtained the medical records of 52 prepubertal patients less than 12 years of age, who were treated for testicular tumors at Seoul National University Children's Hospital (SNUCH) from 1986 to 2010. Among them, the records of 48 patients had complete pathologic and follow-up data, being eligible for review. The various parameters, such as, age at operation (month), initial presentation, duration of initial presentation to diagnosis, pre and post-operative alpha-fetoprotein (AFP), beta-subunit of human chorionic gonadotropin (β-hCG), evaluations for the preoperative metastatic lesions, clinical stage, histological type, adjuvant therapy and its response, and follow-up periods were studied. Diagnosis and treatment algorithm in SNUCH are following: patients suspicious of testicular tumor were assessed by tumor markers (AFP, β-hCG) and scrotal ultrasonography with plain x-rays. In case of suspicious malignancy, abdomen computed tomography (CT) was obtained to evaluate the retroperitoneal lymph node and/or distant metastasis. And then, all patients were conducted radical inguinal orchiectomy and pathologic results were obtained. Further management was determined in accordance with tumor histology and stage. All patients with stage 1 yolk sac tumor were followed with regular measurement of serum AFP levels.

The Statistical Package for the Social Sciences, version 12.0 (SPSS Inc, USA) was used for the statistical analysis. All clinical parameters were analyzed by the Chi-square, Mann-Whiteny U test and are reported as median values with range. *P* value of less than 0.05 was considered to be statistically significant.

RESULTS

A summary of the clinical data of the 48 patients is listed in Table 1. The median age at diagnosis was 19.5 (3-84) months. Three-quarter of patients were presented due to palpable mass and the remained ones were detected by size discrepancy. The former preceded the latter by 5 months in comparison of mean time to diagnosis (2.5 vs 7.5, $p<0.05$).

The tumors were right sided in 21 (44%) boys and left sided in 27 (56%). Preoperative staging indicated that the 45 (93.8%) of patients were localized tumor without lymph node or distant metastasis. Pathology revealed 25 (53%) yolk sac tumor, 17 (36%) teratoma, 2 (4.2%) embryonal carcinoma, 2 (4.2%) epidermoid cyst, 1 (2.1%) mixed germ cell tumor and 1 (2.1%) fibrosarcoma (Table 2). Twenty-three (92%) patients with yolk sac tumor were stage I at the time of diagnosis.

Table 3 shows the comparison of clinical variables between yolk sac tumor and teratoma. Only mean preoperative AFP differed significantly between the two. The AFP level of yolk sac tumor showed significantly higher than that of teratoma. Given that the normal range of AFP is less than 20ng/ml, all patients with yolk sac tumor showed supranormal values, whereas only one patient in teratoma arm showed higher AFP value than norm. The patient was 17 month-old boy and his preoperative AFP at the diagnosis was 39ng/ml.

Median follow-up period was 62 (1-192) months. With regard to the AFP responses of yolk sac tumor, 18 patients (72%) had normalized following radical orchiectomy, 2 patients (8%) showed persistent elevation of AFP and 4 patients (16%) relapsed after normalization of AFP, and 1 patient was lost follow-up during the period of present

study. Median time to relapse of AFP was 8 months (6-12 months). All 6 patients who showed either elevation or relapse of AFP received salvage chemotherapy. This therapy rescued all but 1 patient and the 1 patient were further treated by peripheral blood stem cell transplantation. No patient has experienced relapse after these treatments.

We finished regular follow up of 3 patients who showed no recurrence for more than 10 years. 2 patients are regularly checked with AFP, CPA & testis SONO. There is no AFP elevation for 6 and 8 years. In the most aggressive case, we did peripheral blood stem cell transplantation(PBSCT) after 10 months of orchiectomy. 2 years later, lung metastasis was detected, so we did metastasectomy & 2nd PBSCT. After the treatment, there is no AFP elevation for 6 years. Now, we have regular follow up every year. (Fig.2)

Comparison of mean preoperative AFP between non-relapsed and relapsed patients revealed that AFP of relapsed patients was greater than those of non-relapsed patients (Table 4). Pathologically, five out of six relapsed patients showed the evidence of either vascular invasion or endolymphatic tumor emboli.

Table 1. Demographics of prepubertal patients with testicular tumor

	N=48
Age (mons) at diagnosis	19.5 (3-84)
Presentation	
mass palpation (%)	36 (75.6)
size discrepancy (%)	11 (24.4)
Duration of presentation to diagnosis (mons)	1.5 (1-31)
Laterality	
Right (%)	21 (45.2)
Left (%)	27 (54.8)
Serum tumor markers	
AFP (ng/ml)	369.5 (1-65,200)
hCG (ng/ml)	2.5 (0.01-2,470)
Localization at initial diagnosis	
locallized tumor (%)	44 (93.6)
LN positive (%)	2 (4.3)
distant metastasis (%)	1 (2.1)
AFP response	
normalized (%)	25 (55.8)
relapsed (%)	4 (9.1)
follow-up loss (%)	5 (11.4)
Follow up period (mons)	36 (1-192)

Table 2. Histologic characteristics and age distribution

Histologic type	No. Pts (%)	Median age at diagnosis (mon)
Yolk sac	25 (53.1)	19 (3-39)
Teratoma	17 (36.1)	17 (7-64)
Epidermoid cyst	2 (4.2)	83.5 (83-84)
Mixed GCT	1 (2.1)	55
Fibrosarcoma	1 (2.1)	77

Table 3. Comparison of yolk sac tumor and teratoma (median value)

	Yolk sac	Teratoma	*P* value
Age	19.0 (3-39)	17.0 (7-64)	0.29
Serum AFP	***4600 (20-65200)***	***6.3 (4-39)***	***0.001*** [†]
Serum hCG	2.5 (0.5-7.9)	2.5 (0.1 -2.5)	0.98

[†] : Mann-Whiteny U test

Table 4. Comparison of clinical parameters between recurrence and non-recurrence in yolk sac tumor

	Recurrence	Non-recurrence	*P* value
No. of patients (%)	7 (29.1)	17 (70.9)	N/A
Age at presentation	16 (10-35)	20 (3-39)	0.63
Serum AFP	***7800 (362-36700)***	***3810 (20-65200)***	***0.04*** [†]
Duration (mo) to nadir	52.5 (30-171)	62 (32-110)	0.52

[†] : Mann-Whiteny U test; N/A, not applicable; mo, months

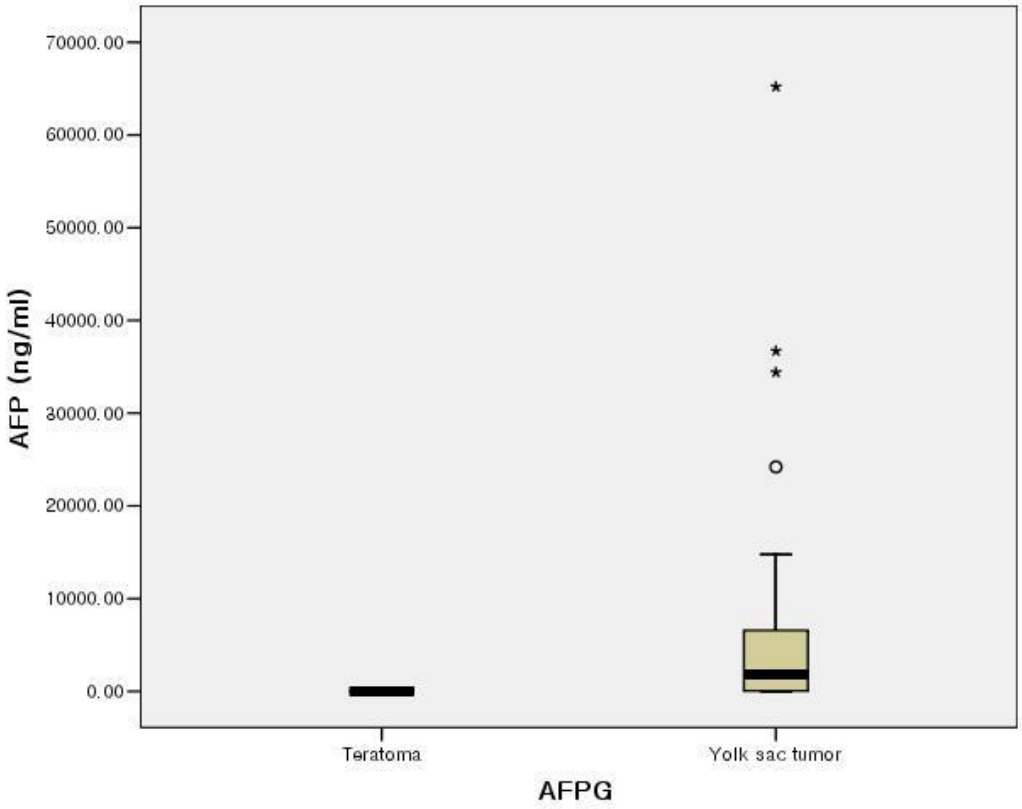

Figure 1. Comparison of preoperative AFP between yolk sac tumor and teratoma

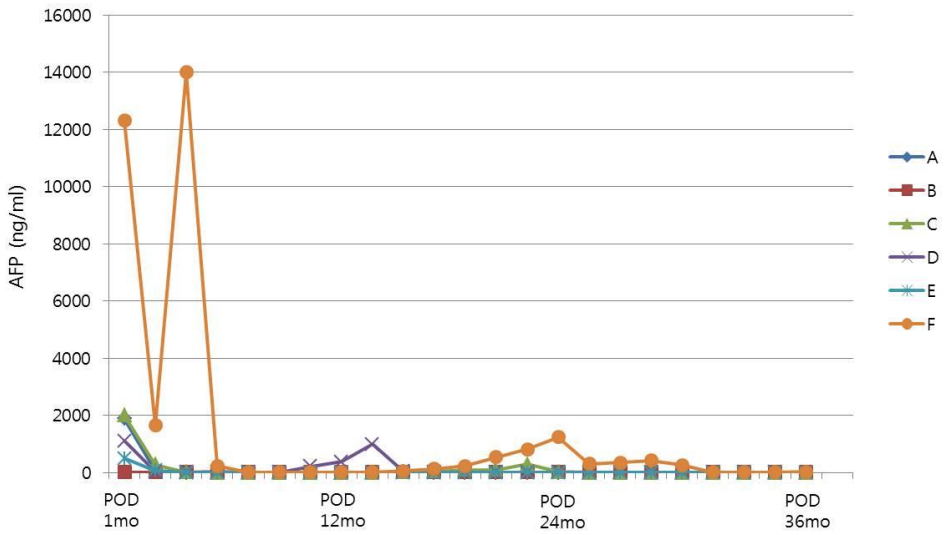

Figure 2. Postoperative AFP patterns in 6 patients who showed persistent elevated or relapsed AFP.

Discussion

This retrospective analysis was conducted in single institutional Korean cohort, which may be useful in reducing reporting bias. Due to the rare worldwide incidence of PTT, we believe that inclusion of our data, despite the small number of cohort, would be the valuable addition to current understanding of PTT. In fact, this study is one of the largest single institutional data of PTT ever reported.

Regarding histological distribution, we confirmed that yolk sac tumor was most prevalent PTT in Korea. Our results are in consistent with that of another multi-institutional Korean study.(9) From the study, the reported rates of yolk sac tumor and teratoma were 48% and 40%, similar distribution to ours, respectively. Moreover, the predominance of yolk sac tumor was reported in Japanese or Taiwanese studies suggesting the predominance of yolk sac tumor in Asian population.(10,11) However, these distributions are in conflict with recently published American data, which showed the larger number of benign teratoma over yolk sac tumor.(3-5) The reason for the discrepancy in histological distribution is still unclear, but some reports provided evidence of racial difference as a possible cause. From the analysis of Surveillance, Epidemiology, and End Results (SEER) data, Walsh et al.(7) found more than 2 fold greater incidence of yolk sac tumor among Asian/Pacific Islanders than whites, whereas no difference in the incidence of teratoma among both ethnic groups. They also reported higher incidence of teratoma than yolk sac tumor in whites and blacks. These may explain the reason of discrepancy of histological distribution among different races. Given the fact that Japanese adults have lower incidence of testis tumor,(8) it is unique that Asian boys are more likely to have yolk sac tumor. Future study will explore what

caused higher incidence of yolk sac tumor in Asian boys.

Our data also revealed that more than 70% of patients were rescued by radical orchiectomy only.) For the remained 6 patients experiencing relapse or persistence of disease, chemotherapy was effective in all but one patient. Although the most aggressive case, there was no need for retroperitoneal lymph node dissection. These contrasted to the reported feature of lymphatic spread and higher metastatic potential of yolk sac tumor in adult counterpart.(12) Prepubertal yolk sac tumors have lower tendency of metastatic disease. Most cases are low stage disease and lymph node is not involved initially. And even if metastasis is presented, it is usually hematogeneous. It means prepubertal yolk sac tumors have lower tendency toward lymphatic metastasis.(13) So routine RPLND or adjuvant chemotherapy are not needed in prepubertal testicular tumors.

In adults, testis tumor is typical example where serum tumor markers play a critical role in diagnosis and management. This is similarly applied to pediatric counterpart and dozens of papers have indicated that AFP has been found to be useful in diagnosing the testis tumor, monitoring the treatment response and detecting recurrence, whereas β-hCG has not.(2,3, 14-16) The present study again confirmed these findings.

Regarding diagnosis, our study underscored the importance of preoperative AFP levels in differentiating yolk sac tumor from teratoma. While all patients with yolk sac tumor showed the elevation of AFP above the reference range (up to 20ng/ml), only one patient with teratoma showed the serum AFP level (39ng/ml) exceeding reference ranges. While there was some overlap of serum AFP level between yolk sac tumor and teratoma, no case of teratoma showed the higher value than 100ng/ml, which was

consistent with the results from Ross et al.(2) If we set 100ng/ml of AFP in differentiating between the two tumors, we would miss only one case of yolk sac tumor confirming the diagnostic value of AFP. This contrasts to other studies, which showed some overlap of APF ranges between the 2 tumors. The reason might be was due to the fact that our teratoma cohort did not include the infant less than 6 months old, which showed physiologic elevation of serum AFP.(17) However, as long as teratoma infrequently affects infants less than 6 months old, the usefulness of AFP in differential diagnosis cannot be denied.

Our results also indicated the usefulness of AFP in monitoring the disease. Following the orchiectomy, six patients who showed the persistence or relapse after normalization of AFP received salvage chemotherapy. This rescued five patients with normalization of AFP. These indicate that measuring AFP only was enough to monitor the fate of testis tumor. While we don't have any solid evidence that elevation of AFP will lead to gross recurrence of yolk sac tumor in PTT, the normalization of AFP after salvage chemotherapy may imply the presence of recurrence and suggest the appropriate management be provided. The importance of monitoring AFP can't be overemphasized in adult's series.(18)

To further know what is related to the patients with relapse, we compared the clinical and pathological characteristics between the relapsed or not to know the predict factors of AFP relapse. Two statistically positive findings were noted. One was that mean preoperative AFP was higher in relapsed patients; however there were considerable overlap between the two, precluding the use of preoperative AFP for predictive purpose. Another was the association of aggressive pathologic behaviors with relapsed patients. It has already been noted that vascular/lymphatic invasion are high-risk factors for

relapse in pure or mixed embryonal carcinoma of adult testis(19) and one Japanese study showed that relapse of yolk sac tumor was associated with the overt invasion of testicular vein.(20) However, our data were the first study to associate the risk of relapse with vascular/lymphatic invasion in PTT. Despite the small number of patients having positive findings, the lack of false positive results would be important in predicting relapse and be helpful in planning follow-up in these low-risk patients.

Some limitation of this study should be mentioned. Due to the small number of specific histology, we did not draw any meaningful conclusion apart from yolk sac tumor and teratoma. In addition, since we only saw the patients with localized yolk sac tumor, we cannot know whether the changes of AFP following treatment might be as good as in yolk sac tumor of other stage. Since the characteristics of tertiary care center, the enrolled patients may not show the histological distribution that can be seen in other hospitals in Korea. Despite all the limitation, we believe that our data would enhance the knowledge of this rare tumor.

Conclusion

Our single center 25 years' experience showed the dominance of yolk sac tumor over teratoma, which is attributable to racial difference that might be originated from genetic factors rather than epidemiologic influence. Compared to adult's counterpart, childhood yolk sac tumor demonstrated more benign course and responded well to chemotherapy even in relapse. In most children, only radical inguinal orchiectromy could be curative. And routine RPLND or adjuvant chemotherapy are not needed. As a differential diagnostic tool, AFP is more useful than image modalities. If AFP is over 100ng/ml, the tumor can be considered closer to the YST than teratoma. So in this case, testis sparing is not indicated. Relapsed yolk sac tumor often showed aggressiveness on pathologic examination and AFP was found to be the most useful marker in the diagnosis and follow-up of childhood yolk sac tumor.

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초 록

서론:

소아의 고환암은 유병률이 매우 낮은 질환으로 그 동안 이에 대한 진단 및 치료알고리즘은 성인의 고환암에 미루어 시행해 왔다. 그러나 성인의 질병과는 병리 특징 및 임상적 과정이 매우 달라 소아 고환암에 대한 정립이 필요한 실정이다. 이에 우리는 지난 20여년 간의 단일 술자에 의한 소아 고환암의 임상적, 병리적 특징을 분석하여 연구해 보고자 하였다.

방법:

1986년부터 2010년까지 고환암으로 진단되어 수술을 시행한 48명의 환아의 의무기록을 후향적으로 분석하였다. 모든 환아들은 근치적 고환 적출술을 시행하였다. 환아의 나이, 임상 양상, 병리적 특징, 종양 표지자의 동역학적인 양상, 치료 결과 등에 대해서 분석하였다.

결과:

진단시 평균연령은 19.5 (3-84)개월이었다. 환아의 주소는 고환 종물이 촉지되어 내원하는 경우가 76%, 양쪽 고환의 크기가 달라서 내원하는 경우가 24%를 차지하였다. 양쪽 고환의 크기가 달라서 내원하는 경우가 고환 종물이 촉지되어 내원하는 경우보다 진단이 5개월 늦었다. 병리적으로는 난황낭 종양이 53%, 기형종이 36%를 차지하였다. 수술전 AFP 수치는 난황낭 종양이 기형종에 비해 매우 높았고(4,600 ng/ml vs, 6.3ng/ml), 기형종에서는

1명의 환아만이 수술전 AFP 수치가 20 ng/ml 이상이었다. 근치적 고환적출술을 시행한 이후 난황낭 종양 환자의 72%는 AFP 수치가 정상화 되었고, 8%는 지속적으로 높은 수치를 보였으며, 16%는 일시적으로 정상화 되었다가 다시 상승하였다. AFP 수치가 정상화되지 않은 환자들의 수술전 AFP은 정상화된 환자들보다 더 높았다. AFP 수치가 정상화되지 않은 6명의 환자중 5명의 환자의 병리 결과 혈관 침범이나 림프종양의 색전 소견을 보였다.

결론:

난황낭 종양 환자가 기형종에 비해 더 많은 수를 차지하고 있는 것으로 나타났다. AFP 은 소아 환자의 난황낭 종양을 진단 및 경과 추적하기에 가장 유용한 도구로 생각된다. 재발하는 난황낭 종양의 경우 병리 소견이 더 악성으로 관찰된다.

주요어: 고환암, 소아, 인종 차이

학 번: 2012-22698