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Original Article

Tumor Markers and Pediatric Intraabdominal Solid Tumors

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Abstract

Background: **There are many tumor markers for initial investigation and diagnosis of pediatric intraabdominal solid tumors (ISTs). However, some types of ISTs cannot be diagnosed by tumor marker examinations because of no specific relationship between the tumor markers and these ISTs.**

Purpose: **The aim of this study was to analyse the relationships between tumor markers and pediatric ISTs.**

Materials and Methods: **A retrospective study of patients with ISTs who were initially treated at Queen Sirikit National Institute of Child Health form June 2015 to December 2016 was conducted. Patient data were collected from the medical records and were selected only among those with the definite diagnosis of ISTs. Tumor markers included neuron-specific enolase (NSE), 24-hour urine of vanillymandelic acid (VMA), serum ferritin, lactase dehydrogenase (LDH), serum alpha-fetoprotein (AFP), beta-human chorionic gonadotrophin (beta-hCG) and cancer antigen 125 (CA125). Information of the tumor markers and each type of ISTs were studied in order to demonstrate the relationships by using statistical analysis with SPSS program. The level of p-value less than 0.05 was considered significant.**

Results: **Thirty-six patients with ISTs were available for the study. The ISTs were finally definite diagnosis based on pathological reports including neuroblastoma, hepatoblastoma, hematologic tumors and retroperitoneal teratoma in 12 (33.3%), 6 (16.7%), 5 (13.9%) and 4 (11.1%), respectively. The 9 remaining ISTs were Wilms' tumor (3), ovarian dysgerminoma (2) and others (4). NSE over 130 ng/ml and urine VMA over 2 mg/day were statistically significant for definite diagnosis of neuroblastoma (p = 0.033, 0.034). NSE level might elevate in ovarian dysgerminoma, Wilms' tumor, lymphoma and leukemia but it was not statistically significant ($p > 0.05$). Increased NSE, 24-hour urine VMA and serum ferritin levels demonstrated a relationship to the severity of neuroblastoma both advanced stage and poor prognosis but no statistical significance. An elevation of LDH level might be found in many ISTs, but it revealed a significant relationship to ovarian dysgerminoma and N-myc amplification of neuroblastoma. High level of beta-hCG and CA 125 were observed in ovarian dysgerminoma. Marked elevation of average AFP level of 653,538 ng/ml was strongly indicated in diagnosis of hepatoblastoma (p = 0.01).**

Conclusion: **NSE over 130 ng/ml and urine VMA over 2 mg/day had a significant relationship to diagnosis of neuroblastoma. Marked elevation of LDH level was significantly demonstrated N-myc amplification of neuroblastoma and ovarian dysgerminoma. Marked elevation of AFP level was a strong indicator for diagnosis of hepatoblastoma in pediatric patient with ISTs.**

Keywords: **Tumor markers, intraabdominal solid tumors**

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Introduction

Three most common intraabdominal solid tumors (ISTs) include neuroblastoma, Wilms' tumor and hepatoblastoma. Incidences of these tumors are 1:75,000-100,000, 7.9:1,000,000 and 0.6-1.2:1,000,000 populations in neuroblastoma, Wilms' tumor and hepatoblastoma, respectively[1-3]. Most of the patients present the symptomatologies with abdominal mass, abdominal distension, weight loss, etc. Investigations with blood examinations, radiological procedures and tissue biopsy for histopathology are performed in order to confirm the definite diagnosis. In this era, tumor markers are influenced in diagnosis of various types of malignant tumors. A tumor marker is a biomarker found in blood, urine and body tissues that can be elevated by the presence of one or more types of cancer[4,5]. Therefore, tumor markers are used to help diagnosis of malignant tumors instead of tissue biopsy in some types of tumor.

However, we had an experience in misdiagnosis of ISTs due to confidence in a tumor marker. An infant with ISTs had mild elevation of serum alpha-fetoprotein (AFP) and moderate elevation of serum neuron specific enolase (NSE) and 24-hour urine vanillylmanadelic acid (VMA) levels. She was diagnosed with neuroblastoma without tissue biopsy and initially treated with chemotherapy. The patient did not improve and the tumor became larger. The diagnosis was changed from neuroblastoma to hepatoblastoma after confirmation of tissue biopsy and pathological report. Herein, we were interested to study the relationships between tumor markers and various types of ISTs in pediatric patients at our institute.

Materials and Methods

This was a retrospective study of all pediatric patients, aged 0-15 years, with ISTs, who were initially treated at Queen Sirikit National Institute of Child Health from June 2015 to December 2016. Patient data were collected from the medical records and were selected only among those with the diagnosis of ISTs and tumor markers including NSE, 24-hour urine VMA, serum ferritin, lactase dehydrogenase (LDH), AFP, beta-human chorionic gonadotrophin (beta-hCG) and cancer antigen 125 (CA 125). We excluded patients who had indefinite diagnosis from the pathological reports and patients surgically treated from other hospitals. Normal levels of tumor markers mentioned in this study were the normal levels used at our institute.

Information of the tumor markers and each type of ISTs were studied in order to demonstrate the relationships by using SPSS version 20 (IBM® SPSS statistic). Correlations between categorical variables were evaluated by Chi-square test and ANOVA. A *p*-value of less than 0.05 was considered significant.

The study was approved by the Ethic Committees of our institute, Document No. 60-041.

Results

During the study period, 48 new patients with intraabdominal tumors admitted for investigation and treatment. Twelve cases were excluded because of presence of cystic abdominal tumors (10) and indefinite diagnosis (2). Therefore, 36 cases with intraabdominal solid tumors were enrolled in the study (Figure 1).

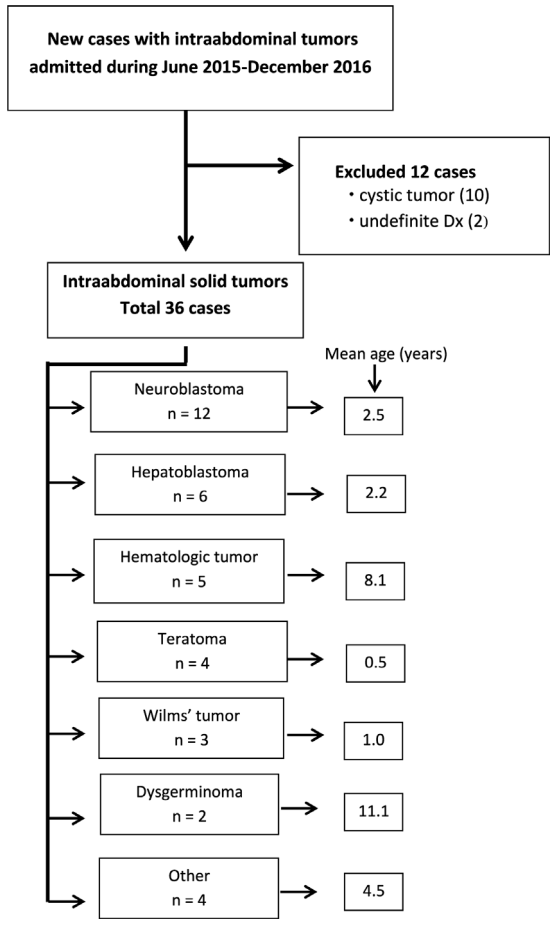

Figure 1 Schematic diagram of patients with intraabdominal solid tumors

These tumors included neuroblastoma 12 cases, hepatobastoma 6 cases, hematologic tumors 5 cases (lymphoma = 4 and acute lymphoblastic leukemia = 1), retroperitoneum teratoma 4 cases (mature =3, immature = 1), Wilms' tumor 3 cases, dysgerminoma 2 cases and others 4 cases (liver sarcoma, rhabdoid tumor of the kidney, rhabdomyosarcoma of urachus and inflammatory myofibroblastic tumor of the pancreas, one case each).

Mean age of the patients varied along with each type of tumors (Figure 1). Teratoma, Wilms' tumor, hepatoblastoma and neuroblastoma occurred in infants and young children with the mean age of 0.5, 1.0, 2.2 and 2.5 years, respectively. Hematologic tumors, rhabdomyosarcoma and dysgerminoma were present in older children with mean age of 8.1, 9.5 and 11.1 years.

Common clinical presentations of these ISTs were palpable abdominal mass in 15 cases and (41.7%), abdominal pain 7 cases (19.4%), and abdominal distension in 9 cases (25%). Three patients (8.3%) had a history of fever and 2 patients had a diagnosis of myocarditis and bony metastasis from neuroblastoma.

Normal level of each tumor marker at our institute and mean tumor marker level of each type of ISTs were shown in Table 1. Of the 12 patients with neuroblastoma, mean levels of serum NSE and urine VMA elevated more than normal levels with statistical significance ($p = 0.020$ and $p = 0.010$). Serum NSE and 24-hour urine VMA levels were the tumor markers

Table 1 Mean levels of various tumor markers for each type of intraabdominal solid tumors (N = 36)

Tumor markers / Types of tumor (n)	NSE Normal 16.3 ng/ml	AFP Normal 12 ng/ml	LDH Normal 344 U/L	Ferritin Normal 10-160 ng/ml	urine VMA Normal 2-7 mg/day
Neuroblastoma (12)					
Mean (sd)	662.9 (717.1)	7.7 (13.4)	3,305.5 (4270.8)	346.8 (286.7)	23.5 (23.9)
p-value*	0.020	0.312	0.350	0.160	0.010
Hepatoblastoma (6)					
Mean (sd)	31.7 (12.7)	652,528 (997,030)	541.3 (66.4)	102.5 (90.4)	2.3 (2.4)
p-value*	0.128	0.001	0.121	0.104	0.310
Hematologic tumor (5)					
Mean (sd)	187.8 (153.6)	1.2 (0.48)	2956.6 (3027.4)	135.2 (128.3)	1.5 (0.21)
p-value*	0.640	0.590	0.770	0.260	0.450
Teratoma (4)					
Mean (sd)	42.3 (33.0)	539.1 (18.0)	722 (239.5)	163.3 (39.8)	0.6 (0.14)
p-value*	0.330	0.590	0.340	0.550	0.410
Dysgerminoma (2)					
Mean (sd)	474.7 (23.0)	1.9 (0.36)	8,667 (6448.8)	695.4	3.2 (0.42)
p-value*	0.660	0.710	0.008	-	0.530
Wilms' tumor (3)					
Mean (sd)	190.6 (36.9)	7 (8.7)	2,435.6 (328.6)	191.6 (191.1)	2.9 (1.64)
p-value*	0.650	0.900	0.850	0.290	0.590
Rhabdoid tumor (1)					
Mean	88.2	5.5	1,678	299.6	-
Liver sarcoma (1)					
Mean	21.3	0.89	580	628.3	0.2
IMT (1)					
Mean	48.5	1.97	620	38	1.7
RMS (1)					
mean	21.4	1.8	1,424	491.2	2.6

*p-value by unpaired t-test; compared with other tumors grouped together

Table 2 Levels of NSE and 24-hour urine VMA for the diagnosis of neuroblastoma (12 cases) compared with non-neuroblastoma (24 cases)

Levels of tumor marker	Sensitivity (%)	Specificity (%)
NSE (ng/ml)		
16.3	100 (12/12)	0 (0/24)
120	66.7 (8/12)	70.8 (17/24)
130	66.7 (8/12)	75.0 (18/24)
24- hour urine VMA (ng/day)		
1.5	91.6 (11/12)	58.3 (14/24)
2	83.3 (10/12)	70.8 (17/24)
7	53.3 (7/12)	100 (24/24)

used for diagnosis of neuroblastoma. For analysis of our 36 ISTs, serum NSE level over normal limit (>16.3 ng/ml) had the sensitivity of 100% for neuroblastoma, but there was no specificity for other tumors because serum NSE level elevated over 16.3 ng/ml in every type of ISTs. Serum NSE level step up to 130 ng/ml was statistically significant for definite diagnosis of neuroblastoma (sensitivity 66.7%, specificity 75.0%, $p = 0.033$).

Evaluation of 36 patients with ISTs, an upper normal limit of 24-hour urine VMA (> 7 mg/day) had the sensitivity of 58.3% for patients with neuroblastoma and specificity of 100% with other tumors ($p = 0.000$). If we chose the lower limit of 24-hour urine VMA (>2 mg/day) for analysis, there were 83.3% sensitivity and 70.8% specificity ($p = 0.034$) (Table 2).

Therefore, significant value for diagnosis of neuroblastoma were serum NSE level over 130 ng/ml ($p = 0.033$) and 24-hour urine VMA over 2 ng/day ($p = 0.034$). Serum NSE level might elevate in ovarian dysgerminoma, Wilms' tumor, lymphoma and leukemia, but it was not statistically significant ($p > 0.05$). The level of 24-hour urine VMA might elevate in hepatoblastoma, dysgerminoma and Wilms' tumor but it was not significantly different ($p > 0.05$). AFP level markedly elevated in hepatoblastoma with the mean level of 652, 528 ng/ml ($p < 0.001$), while LDH level elevated in ovarian dysgerminoma with the mean level of 8,667 U/L ($p = 0.008$). Every tumor marker had no significant relationship to definite diagnosis of Wilms' tumor, rhabdoid tumor of kidney, retroperitoneal teratoma, liver sarcoma, rhabdomyosarcoma, lymphoma, leukemia and inflammatory myofibroblastic tumor of pancreas ($p > 0.05$).

Table 3 showed correlation of tumor markers

Table 3 Mean levels of tumor markers and clinical risks of neuroblastoma

Tumor markers / Neuroblastoma (N =12)	NSE Normal 16.3 ng/ml	AFP Normal 12 ng/ml	LDH Normal 344 U/L	Ferritin Normal 10-160 ng/ml	Urine VMA Normal 2-7mg/day
Stage					
2 (n=1) Mean	29.7	1.4	442	88.5	1.2
3 (n=4) Mean (sd)	633.2 (1037)	7.9 (5.2)	3942.5 (6385.3)	128.7 (111.5)	12.7 (17.3)
4 (n=7) Mean (sd)	770.4 (569.3)	10.4 (18.8)	3350.7 (3378.5)	477.2 (279.4)	32.9 (25.1)
p-value*	0.839	0.668	0.798	0.130	0.270
Risk					
Low (n=1) Mean	29.7	1.4	442	88.5	1.2
Intermediate (n=4) Mean (sd)	309.1 (398.1)	8.2 (3.9)	1344.2 (1216.1)	213.2 (257.9)	17.5 (16.7)
High (n=7) Mean (sd)	955.5 (783.1)	9.6 (19.1)	4835.2 (5102.9)	441.0 (290.5)	30.1 (27.3)
p-value*	0.250	0.885	0.328	0.366	0.477
N-myc					
non-amplification (n= 7) Mean (sd)	334.7 (349.8)	6.0 (4.6)	1221.2 (931.2)	326.3 (325.5)	19.7 (20.4)
Amplification (n=4) Mean (sd)	1282.4 (1081.5)	17.1 (27.2)	6970.3 (6552)	286.7 (136.7)	23.3 (34.5)
p-value*	0.058	0.332	0.039	0.885	0.837

***p-value by one-way ANOVA**

with clinical risks of neuroblastoma. NSE, ferritin and 24-hour urine VMA levels trended to elevate without statistical significance in neuroblastoma stage 3 and 4, intermediate and high risk groups and patients with positive N-myc amplification. LDH level elevated in advanced stages, intermediate and high risk groups of neuroblastoma, especially marked elevation of LDH level in N-myc amplification ($p = 0.039$). Elevation of serum ferritin level had the relationship to all stages of neuroblastoma by 72% sensitivity and increased to 100% sensitivity in stage 4 neuroblastoma. High ferritin level was noted in every case of neuroblastoma stage 3 and stage 4. Ferritin level elevated over 150 ng/ml in all 7 cases with neuroblastoma stage 4.

Special tumor marker investigations of ovarian dysgerminoma were beta - hCG (normal level < 5 m IU/ml) and CA 125 (normal level < 35 U/ml). Of our 2 patients with dysgerminoma, beta - hCG were 117.8 and 53.3 m IU/ml and mean level 85.5 m IU/ml. While, CA 125 was 81 and 470 U/ml, mean level 275.5 U/ml.

Discussion

This study showed the incidence of ISTs at our institute which neuroblastoma, hepatoblastoma and hematologic cancers were the three most common tumors. These findings were contrast from the previous studies[1-3] because this study was done in a short period of time and did not represent large amounts of ISTs. However, age incidences of each type of tumors were similar to the previous studies[1-3].

NSE is a neuronal form of glycolytic enzyme which was originally extracted from bovine brain. It was later found in endocrine (APUD - amine precursor uptake and carboxylation) cells of the central and peripheral divisions of the diffuse neuroendocrine system. Tumors of the APUD system or APUDomas, that can produce NSE, are islet cell tumor, pheochromocytoma, medullary thyroid tumor, neuroblastoma and APUD tumors of gut and lung[6].

NSE was detected in small cell lung cancer[6]. High serum level of this tumor marker had relationship to stage and disease course of neuroblastoma[7,8]. Nowadays, NSE is the principal tumor marker for diagnosis and prognostic predictor of neuroblastoma[8,9]. Zeltzer[8] chose a cutoff point of 100 ng/ml of NSE level to show the difference in survival of neuroblastoma, while the level of NSE over 15 ng/ml was defined as abnormal. Patients with NSE levels between above and below 100 ng/ml were significantly different. From this study, we choose the cutoff point of NSE level at 130 ng/ml to have the relationship to diagnosis and survival ($p = 0.033$), while NSE level over 16.3 ng/ml, at our institute, was defined as abnormal but not significant. Serum NSE level in patient with neuroblastoma was proven to have relationship to stage and disease course. Zeltzer[9] revealed elevation of serum NSE level correlation to high staging with significance and decreased NSE level in patients with response to therapy. In patients with stage IV-S disease, serum NSE level was significantly lower than those in stage IV. This result might confirm that stage IV-S had a more benign clinical course. Our present study revealed high NSE level in stage 3 and 4 of neuroblastoma and there was significantly higher NSE level in N-myc amplification than those with non-amplification.

From the present study, serum NSE level elevated over 100 ng/ml in the patients with ovarian dysgerminoma, Wilms' tumor, lymphoma and leukemia without statistical significance. Odelstad[10] used NSE to be a marker for differential diagnosis of neuroblastoma and Wilms' tumor. Tsuchida[11] suggested that serial determination of serum NSE could be differential diagnosis of neuroblastoma and other pediatric tumors because of its specificity and sensitivity.

VMA is one of intermediate products of catecholamine which excretes in the urine. Elevation of 24-hour urine VMA level has relationship to adrenal tumors, especially neuroblastoma and pheochromocytoma. Approximately 90-95% of patients with neuroblastoma showed high level of 24-hour urine VMA[12,13]. This study demonstrated that almost all of our patients with neuroblastoma had elevation of 24-hour urine VMA (range 1.2-63.2 ng/day and mean level 23.5 ng/day, $p = 0.010$). It slightly elevated in dysgerminoma, Wilms' tumor and rhabdomyosarcoma, but no significance. We used the cutoff level of 24-hour urine VMA of over 2 mg/day for significant diagnosis of neuroblastoma (sensitivity 83.3%, specificity 70.8%, $p = 0.034$).

Zeltzer[8] reported elevation of serum NSE in children with metastatic neuroblastoma. Our study revealed serum NSE, ferritin, LDH and 24-hour urine VMA levels elevated in neuroblastoma with high stage,

high risk and N-myc amplification, but no significance, except correlation of high LDH level to N-myc amplification ($p = 0.039$).

Serum AFP level was significantly high in our six cases with hepatoblastoma. It also elevates in normal infants under eight months of age and malignant germ cell tumors. However, small cell undifferentiated hepatoblastoma does not associate with elevated serum AFP[3]. Elevation of LDH level is not specific to diagnose any ISTs, but it demonstrated a high level with statistical significance in our two cases with ovarian dysgerminoma. LDH level usually elevates in tumors with high turnover rate, such as dysgerminoma, malignant hematologic tumors, seminoma and advanced stages of neuroblastoma[14,15].

Tumor markers for ovarian tumors are beta-hCG and CA 125 that correlates to epithelial cell type of ovarian malignancy. Both tumor markers elevated in our two patients with dysgerminoma. Beta - hCG level slightly elevates in dysgerminoma, but it markedly elevates in choriocarcinoma[16].

Ferritin level was found to increase significantly in our both cases of dysgerminoma and had a trend to elevate in high stage and high risk neuroblastoma. Our 7 patients with stage 4 neuroblastoma had the ferritin level increased over 150 ng/ml. Silber[17] reported that ferritin level over 150 ng/ml had a relationship to metastatic neuroblastoma and prediction of a poor prognosis.

This study has some limitations because it was a retrospective study conducted in a short period of time. Only 36 patients were enrolled in the study. Some types of ISTs had a small amount so patient data could not be well analyzed. Further study should be performed.

Conclusion

The present study revealed serum NSE level over 130 mg/ml and 24-hour urine VMA level over 2 mg/day had a relationship to diagnosis of neuroblastoma with statistical significance. Both tumor markers trended to increase levels in high stage and high risk neuroblastoma but there was no statistical significance. Serum NSE level also elevated in dysgerminoma, Wilms' tumor, lymphoma and leukemia. Marked elevation of AFP level had significant relationship to hepatoblastoma. AFP level slightly elevated in teratoma and normal infant. LDH level was significantly high in ovarian dysgerminoma and N-myc amplification neuroblastoma. Ferritin level elevated in every case of stage 3 and stage 4 neuroblastoma. Beta-hCG and CA125 levels were higher than normal limit in ovarian dysgerminoma.

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บทคัดย่อ **สารส่อมะเร็งและก้อนเนื้องอกในช่องท้องของเด็ก**

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**กลุ่มงานศัลยศาสตร์ สถาบันสุขภาพเด็กแห่งชาติมหาราชินี กรุงเทพฯ*

ความเป็นมา: มีสารส่อมะเร็งหลายชนิดที่ใช้ตรวจเบื้องต้นเพื่อวินิจฉัยก้อนเนื้องอกในช่องท้องของเด็ก อย่างไรก็ตาม เนื้องอกบางชนิดไม่สามารถให้การวินิจฉัยได้โดยการตรวจจากสารส่อมะเร็งเพราะว่าไม่มีความสัมพันธ์เฉพาะระหว่างสารส่อมะเร็งกับชนิดของเนื้องอกเหล่านี้

วัตถุประสงค์: เพื่อวิเคราะห์หาความสัมพันธ์ระหว่างสารส่อมะเร็งกับก้อนเนื้องอกในช่องท้องของเด็ก

วัสดุและวิธีการ: เป็นการศึกษาย้อนหลังในผู้ป่วยเด็กที่ป่วยเป็นโรคก้อนเนื้องอกในช่องท้องที่รักษาครั้งแรกในสถาบันสุขภาพเด็กแห่งชาติมหาราชินี ตั้งแต่เดือนมิถุนายน 2548 ถึง ธันวาคม 2549 ข้อมูลของผู้ป่วยถูกรวบรวมจากเวชระเบียนและเลือกเฉพาะผู้ป่วยที่ได้รับการวินิจฉัยได้ถูกต้อง สารส่อมะเร็งที่ศึกษาได้แก่ neuron specific enolase (NSE), vanillylmandelic acid (VMA) ในปัสสาวะที่เก็บใน 24ชั่วโมง serum ferritin lactic dehydrogenase (LDH), alpha-fetoprotein (AFP) beta-human chorionic gonadotrophin (beta-HCG) และ cancer antigen 125 (CA125) ข้อมูลของสารส่อมะเร็งและก้อนเนื้องอกในช่องท้องแต่ละชนิดถูกนำมาศึกษาเพื่อแสดงให้เห็นถึงความสัมพันธ์ระหว่างกันโดยการวิเคราะห์ทางสถิติด้วยโปรแกรม SPSS กำหนดให้ p-value น้อยกว่า 0.05 มีนัยสำคัญทางสถิติ

ผล: ผู้ป่วย 36 รายที่มีก้อนเนื้องอกในช่องท้องถูกนำมาศึกษาในครั้งนี้ ก้อนเนื้องอกที่ได้รับการวินิจฉัยขั้นสุดท้ายยืนยันจากรายงานผลการตรวจทางพยาธิวิทยา ประกอบด้วย neuroblastoma 12 ราย (ร้อยละ33.3), hepatoblastoma 6 ราย (ร้อยละ16.7), hematologic tumors 5 ราย (ร้อยละ13.9) ก้อนเนื้องอกในช่องท้องที่เหลืออีก 9 ราย ได้แก่ Wilms' tumor (3 ราย), ovarian dysgerminoma (2 ราย) และเนื้องอกอื่นๆ (4 ราย) ระดับ NSE ที่สูงกว่า 130ng/ml และ VMA ในปัสสาวะ 24 ชั่วโมงสูงกว่า 2 mg/day สามารถใช้ในการวินิจฉัย neuroblastoma อย่างมีนัยสำคัญทางสถิติ ($p = 0.033$ และ $p = 0.034$) ระดับของ NSE อาจสูงขึ้นใน ovarian dysgerminoma, Wilms' tumor, lymphoma และ leukemia แต่ไม่มีนัยสำคัญทางสถิติ ($p > 0.05$) การสูงขึ้นของระดับ NSE, VMA และ serum ferritin แสดงให้เห็นถึงความสัมพันธ์กับความรุนแรงของ neuroblastoma ทั้งระยะที่แพร่กระจาย และบอกถึงการพยากรณ์โรคที่ไม่ดี แต่ไม่มีนัยสำคัญทางสถิติ การเพิ่มขึ้นของระดับ LDH อาจจะพบในผู้ป่วยก้อนเนื้องอกของช่องท้องหลายชนิด แต่จะมีความสัมพันธ์อย่างมีนัยสำคัญกับ ovarian dysgerminoma และ neuroblastoma ชนิดที่พบ N-myc amplification การสูงขึ้นของค่า beta-HCG และ CA125 พบใน ovarian dysgerminoma ระดับ AFP ที่สูงค่าขึ้นอย่างมาก โดยมีค่าเฉลี่ย 653,538 ng/ml ในการศึกษาครั้งนี้เป็นการบ่งชี้ยืนยันการวินิจฉัยโรค hepatoblastoma อย่างเด่นชัด ($p = 0.01$)

สรุป: ค่า NSE ที่สูงกว่า 130 ng/ml และ VMA ในปัสสาวะ 24 ชั่วโมงสูงกว่า 2 mg/day มีความสัมพันธ์ในการวินิจฉัย neuroblastoma อย่างมีนัยสำคัญ ค่า LDH ที่สูงมาก แสดงถึงความสัมพันธ์กับ neuroblastoma ชนิดที่มี N-myc amplification และ ovarian dysgerminoma การสูงขึ้นอย่างมากของระดับ AFP เป็นเครื่องบ่งชี้ถึงการวินิจฉัย hepatoblastoma ในผู้ป่วยที่มาด้วยก้อนเนื้องอกในช่องท้องเด็ก